RADIOLOGY

A MONTHLY JOURNAL DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

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RADIOLOGY

A MONTHLY PUBLICATION DEVOTED TO CLINICAL RADIOLOGY AND ALLIED SCIENCES

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Vol. 74 JUNE 1960 No. 6

Neoplasia Following Therapeutic Irradiation for Benign Conditions in Childhood[1]

EUGENE L. SAENGER, M.D., FREDERIC N. SILVERMAN, M.D., THEODOR D. STERLING, Ph.D., and MALCOLM E. TURNER, Ph.D.[2]

THE QUESTION OF whether or not radiation can be indicted as the principal causative factor in the induction of neoplasia following radiation exposure for either diagnostic or therapeutic purposes has been of increasing interest over the past several years (4, 12, 18, 19, 20). The present investigation was initiated in 1956, in the Cincinnati area, which appeared to offer abundant material for evaluation. The first case of x-irradiation for treatment of "enlarged thymus" was reported from Cincinnati by Friedlander in 1907 (8), and both roentgen diagnosis and therapy of thymic enlargement enjoyed considerable local popularity until recently. Observations from this city were published by Lange in 1914 (11). Since the majority of patients in the series to be reported here were from a group of private and municipal hospitals, none of which is particularly noted as a cancer center, the possibility of bias being introduced by selection of a neoplasia-prone population was thought to be minimal.

HISTORICAL REVIEW

At the time of Friedlander's report, there was considerable medical interest in thymic enlargement as a manifestation of status thymicolymphaticus, a so-called constitutional disorder associated with a tendency to respond catastrophically to minor noxious stimuli. A large thymus was commonly described as necropsy in children who died suddenly, apparently as a result of diminished resistance from status thymicolymphaticus. Moreover, concern was voiced over the possibility of suffocation by tracheal compression resulting from the enlarged gland. X-irradiation, then recently available, seemed to provide not only the means to treat the enlarged thymus but also a method for its detection. It is interesting to note, however, that in Friedlander's case the enlargement was detected by palpation in the suprasternal notch and by percussion! Routine diagnostic x-ray examinations were undertaken among children in whom the risks of sudden death or suffocation seemed greatest: the newborn and those undergoing anesthesia, most frequently for tonsillectomy and adenoidectomy. A wide mediastinal shadow was often the indication for the application of therapeutic radiation even in the absence of signs or symptoms of disease.

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[1] From the Departments of Radiology, Pediatrics, and Preventive Medicine, University of Cincinnati, College of Medicine and Children's Hospital, Cincinnati, Ohio. Presented at the Forty-fifth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov. 15–20, 1959.

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It is clear that unfamiliarity with available standards misled those gauging thymic enlargement on the basis of weight, while the total absence of adequate standards was disregarded by those who used roentgenographic size as an index of abnormality. The anatomic weight standards of Hammar (9) and of Boyd (2) clearly showed that 50 to 90 per cent of normal healthy children have thymus glands weighing more than the "accepted upper limit" of 20 gm. The rapid decrease in cell population and size of lymphoid structures with many types of stressful stimuli was not appreciated; and there was practically no knowledge of the equally rapid recovery of thymic weight after acute illness. Thus, children dying after chronic illness were found to have acceptably small thymus glands, whereas those who died suddenly, in good nutritional status, demonstrated "enlarged" thymus glands which too often satisfied medical curiosity as to the cause of the fatal outcome and prevented further search for inapparent infections or other factors leading to sudden death.

At the same time, mediastinal width as measured on the roentgenogram was used as an index to thymic enlargement without regard for extrinsic and intrinsic factors modifying the radiographic shadow. The dynamic concept of width in relation to respiratory phase was undeveloped. The fact that equipment then available did not permit the technician to choose optimal times in the respiratory cycle for exposure gave a statistical advantage to the expiratory phase with respect to the relatively brief inspiratory phase. Of special importance was the practice of taking chest films with the infant in the dorsal recumbent position at short tube distances. In brief, all the factors which produce maximal physiologic widening of the mediastinal shadow combined to indicate abnormality to the radiologist whose standard of reference was the relatively well defined mediastinum of a co-operative adult as shown in good inspiration on an erect teleroentgenogram.

The first indication that adverse reactions to thymic irradiation can occur was the report in 1949 of Scharnagel and Pack (17) of a five-year-old boy in whom basal-cell epitheliomas developed exactly in the area of the entrance port through which he had received x-irradiation to his thymus shortly after birth. Although no dose was specified, cutaneous changes developed promptly not only over the port anteriorly but also over the skin of the back and axillary regions. In 1950, Duffy and Fitzgerald (6) noted that 9 of 28 children who were seen for cancer of the thyroid had had prior irradiation to the thymus in early life (fourth to sixteenth month). In 1955, Clark (3) reported that all of 15 cases of thyroid carcinoma in children fifteen years of age or younger which he had seen had been preceded by x-ray therapy in infancy and early childhood for benign conditions about the head, neck, and chest. Simpson *et al.* (19) reported a statistically significant difference in the incidence of thyroid carcinoma in individuals irradiated as children for "thymic enlargement" as compared with their unirradiated siblings and with national statistics for the incidence of thyroid carcinoma. Other reports (7, 13, 16, 23) supported the association, although dissenting opinions or reservations have been expressed on the basis of surveys similar in nature if not in degree (20, 22). In only one series (4) in which the numbers compare with those in the report of Simpson *et al.* were no adverse effects of radiation to be found.

MATERIALS AND METHODS

Earlier studies (4, 12, 19, 20) were carried out primarily by questionnaires filled out by patients or relatives. Telephone and personal interviews supplemented this technic. The basic plan of these studies was designed to answer the following questions:

1. Has the child been irradiated?
2. Have any neoplasms been found in the child?
3. Have any neoplasms been found in the unirradiated siblings?

In our study it was deemed important to have each family interviewed by a nurse familiar with the field of radiation therapy and with special training in public health aspects of nursing. Three such interviewers were so employed. The population at risk was chosen from records of four Cincinnati hospitals. The numbers of patients and siblings from the hospital populations are shown in Table I. Cincinnati General Hospital is a municipal hospital operated by the City of Cincinnati for the care of the indigent population of the city and is the major teaching hospital of the University of Cincinnati College of Medicine. The Children's Hospital is a private hospital which forms an integral part of the University Medical Center in Cincinnati. In association with this hospital is a large outpatient clinic catering to an indigent and semi-indigent population both from the City of Cincinnati and the many surrounding communities. This hospital forms the major private pediatric service for the city. The Bethesda Hospital is a general hospital for private patients, with a large maternity service. Good Samaritan Hospital is a large general hospital, with maternity and pediatric services.

TABLE I: DISTRIBUTION OF PATIENTS AND FAMILIES INTERVIEWED

	No.	Per cent*
Total treated patients	2,230	...
Families interviewed	1,512	...
Patients with available histories	1,644	73.7
Interview refused	152	6.8
Patients untraced	434	19.5

* Potential group size = 2,230.

The records of the departments of radiology of each of these several institutions were searched for patients under sixteen years of age who had received x-ray therapy to the head, neck, or chest during 1932 to 1950. The population included those irradiated for thymic enlargement, cervical adenitis, acute and chronic sinusitis, mastoiditis, pneumonitis, enlarged hilar nodes, epilation of the scalp, and other dermatoses about the head and neck. Family health histories were obtained in 1,512 interviews of the 2,230 possible patients. The interviews resulted in the identification and evaluation of 1,644 individuals (73.7 per cent follow-up) who had received roentgen therapy and 3,777 unirradiated siblings as controls. The discrepancy between 1,644 and 1,512 is explained by multiple cases of therapy in families. Four hundred and thirty-four of the original index patients could not be found, and 152 individuals refused interview. Personal interview was obtained in all but 92 of the traced cases. In the 92 families who had left the Cincinnati area, information was provided by having the informant fill out a questionnaire modeled after the interviewer's check list.[3] Ninety-five and seven-tenths per cent of the patients located, therefore, were investigated by personal interview.

All reported neoplasms were verified by inspection of the report of the pathologist, by review of the microscopic section, or by examination of the hospital records. The analysis is restricted to the 1,644 patients and their 3,777 siblings for whom the records were considered adequate.

RESULTS

Description of the Population: The mean age of the patients as of 1956 was 18.4 years and the median age was 18.4 years. The siblings showed a mean age of 18.2 years and a median age of 17.2 years. While the means are very similar, the two distributions appear to be of decidedly different forms. The differences in distribution can be seen from comparison of Figures 1 and 2. The standard deviation for patients is 5.9 years and that of the siblings is 30.8 years. The hypothesis that the two groups were selected from populations with equal variances must be rejected ($F = 5.18$, $df = 1643/3776$, $p < 0.001$). The distribution of patients and siblings in respect to sex and race are shown in Table II.

[3] Copies of the questionnaires, etc., may be obtained from the authors.

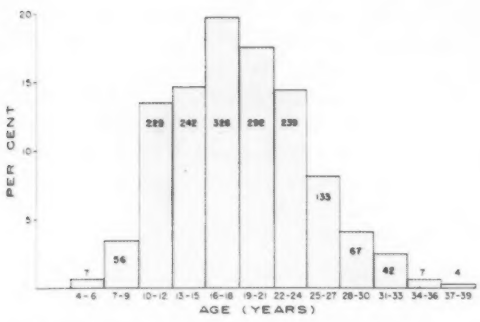

Fig. 1. Age distribution of 1,644 patients.

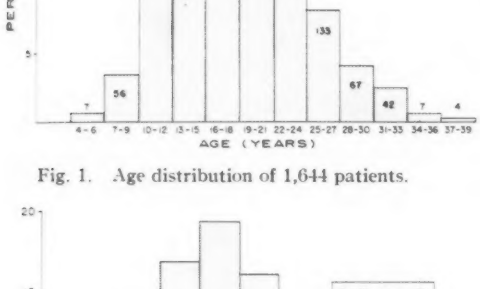

Fig. 2. Age distribution of 3,777 sibling controls. Note the difference in age groupings of patients and controls (abscissa) of Figs. 1 and 2.

TABLE II: SEX AND RACE DISTRIBUTION

	White Male	White Female	Non-white Male	Non-white Female
Patients (1,644)	858 (52.2%)	645 (39.2%)	88 (5.4%)	53 (3.2%)
Siblings (3,777)	1,664 (44.1%)	1,653 (43.8%)	229 (6.1%)	231 (6.0%)

The follow-up period was eleven years or greater for 83 per cent of the patients and over sixteen years for 46 per cent (Table III).

The principal conditions for which radiation therapy was given are shown in Table IV. Thymic irradiation accounted for 33 per cent and cervical adenitis for 26.9 per cent. Of interest is the fact that 21 per cent of the sample received radiation therapy for two or more unrelated conditions.

Because of the many different radiotherapists who treated these children

TABLE III: LENGTH OF FOLLOW-UP FOR 1,644 PATIENTS

Elapsed Time between Irradiation and Interview	No. Patients	Per cent Patients
0–5	24	1.5
6–10	165	10.0
11–15	602	36.6
16–20	474	28.8
21–25	224	13.6
26–30	64	3.9
31–35	1	0.1
Unknown	90	5.5
TOTAL	1,644	100.0

TABLE IV: PRINCIPAL INDICATIONS FOR RADIATION THERAPY

Reason for Irradiation	No. Patients	Per Cent Patients
Enlarged thymus	543	33.0
Cervical adenitis	443	26.9
Hypertrophic tonsils and adenoids	63	3.8
Mastoid	52	3.2
Hypertrophic tissue in fossa of Rosenmueller	8	0.5
Cellulitis and furunculosis of face and neck	27	1.6
Tuberculous adenitis	14	0.9
Bronchitis, bronchopneumonia	129	7.8
Skin disease	20	1.2
Multiple irradiation	345	21.0
TOTAL	1,644	100.0

and the fact that about 15 per cent were treated before the roentgen was established as a dose unit, it is not possible to categorize the many variants of x-ray technics employed. About 57 per cent of patients received therapy with 100 to 140 kvp and 43 per cent at 200 kvp. Appropriate filtration was used: 1 to 4 mm. Al or 0.25 mm. Cu at the lower energy and 0.5 mm. Cu and 1 mm. Al at the higher voltages.

The distribution of doses is shown in Table V; 62 per cent of the group received less than 400 r and 72.5 per cent less than 600 r. In 18.1 per cent of the group there was no record of dose received. Field sizes (Table VI) were less than 50 sq. cm. in 15.6 per cent, from 51 to 75 sq. cm. in 15.3 per cent, and from 76 to 100 sq. cm. in 46.6 per cent. Field size was not specified in 16 per cent.

Malignant Neoplasms: A total of 29 malignant neoplasms were reported, 18

TABLE V: DISTRIBUTION OF DOSES IN PATIENTS

Dose Range (r in air)	No. Patients	Per Cent of Patients	Cumulative Percentage
0–50	67	4.1	4.1
51–200	586	35.6	39.7
201–400	366	22.3	62.0
401–600	172	10.5	72.5
601–800	67	4.1	76.6
801–1,000	28	1.7	78.3
1,001–1,200	28	1.7	80.0
1,201–1,400	10	0.6	...
1,401–2,000	13	0.8	...
2,001–5,000	10	0.6	...
No record	297	18.1	...
TOTAL	1,644	100.0	

TABLE VI: FIELD SIZES IN PATIENTS

Field Size (sq. cm.)	No. Patients	Per Cent Patients	Cumulative Percentage
<50	257	15.6	15.6
51–75	252	15.3	30.9
76–100	766	46.6	77.5
101–200	13	0.8	78.3
201–300	93	5.7	84.0
Unknown	263	16.0	100.0
TOTAL	1,644	100.0	

for the patients and 11 for the siblings. When malignant disease occurring after the age of twenty-three years is eliminated, 17 cases remain in the patient group (Table VII, p. 894): 11 carcinomas of the thyroid, 1 case each of carcinoma of the parotid, submaxillary gland, nasal vestibule, and breast, 1 glioblastoma multiforme of the brain and 1 leukemia. One patient (No. 676) with a malignant teratoma of the ovary had irradiation to the cervical nodes within several weeks of surgery for the teratoma and was not included for statistical analysis.

Among the siblings, 6 cases of malignant neoplasm were found under the age of twenty-one (Table VIII). There were 3 leukemias, a myosarcoma of the leg, a fibrosarcoma of the lip, and an angiosarcoma of the orbit. There were no cases of thyroid cancer.

The expected number of cases of thyroid cancer for a group of 1,644 individuals totaling 30,254 person-years is 0.12 (5, 15). The actual number of thyroid cancers found was 11. The probability of this difference happening by chance alone is extremely small; $p < 0.001$ for the most conservative statistical test. Such a test is based on the assumption that the incidence of thyroid cancer is not known and tests the hypothesis that 11 cases out of 1,644 are a significant departure from 1 case out of 1,644. The expected number of cases of cancer of the thyroid for the sibling group, based on 3,777 individuals and 68,357 person-years, is 0.28 and no cancer of the thyroid was found. The number of thyroid carcinomas for siblings does not disappoint expectation, while the patient group exhibits a 100-fold increase over the expected incidence. In addition to the significance of the thyroid cancers in our series, there was one patient with a carcinoma of the parotid, another with a carcinoma of the submaxillary gland, and a third with a carcinoma of the nasal vestibule. These neoplasms were all probably within the area of original irradiation, and their occurrence is as impressive as that of the thyroid cancers.

TABLE VIII: NONIRRADIATED SIBLINGS (CONTROLS) WITH MALIGNANT NEOPLASMS*

Family Index No.	Sex and Race	Age at Diagnosis (years)	Neoplasm
322	M, W	13	Myosarcoma, left leg
329	M, W	4	Leukemia
1,335	F, W	4	Fibrosarcoma, upper lip
1,447	M, W	19	Leukemia
385	F, W	12	Adenocarcinoma or endothelioma of orbit
82	M, W	16	Leukemia

* Five control siblings are not included in this group. They are a 31-year-old white female with cystadenocarcinoma of the ovary; a 41-year-old white male with adenocarcinoma of undetermined primary site; a 30-year-old white female with basal-cell skin cancer; a 32-year-old white female with carcinoma of cervix *in situ*; and a 35-year-old white female with carcinoma of the breast.

Benign Neoplasms: In the patient group there was a total of 18 benign tumors (Table IX). Seven patients had thyroid adenomas. There were three osteochondromas, 2 being in the upper extremity and 1 in the lower. Five benign breast tumors were found: 4 fibroadenomas and

TABLE VII: PATIENTS WITH MALIGNANT NEOPLASMS FOLLOWING IRRADIATION

Family Index No.	Sex and Race	Age at Time of Therapy	Reason for Therapy	Age at Diagnosis of Neoplasm (years)	Interval Between Irradiation and Diagnosis (years)	Dose (r in air)	Field Size (sq. cm.)	Kilovoltage (kvp)	Target-Skin Distance (cm.)	Filtration (mm.)	Types of Neoplasm
416	M, W	6 yr.	Cervical adenitis	13	7	450	78.5	120	35	4 Al	Carcinoma thyroid
422	F, W	4 yr.	Cervical adenitis	15	11	180	38.5	140	40	4 Al	Follicular adenocarcinoma thyroid
743	F, W	2 days	Thymus	20	20	100	78.5	140	50	3 Al	Cystadenocarcinoma thyroid
744	F, W	2 wk.	Thymus	11	11	390	78.5	200	50	0.5 Cu + 1 Al	Carcinoma thyroid
798	F, W	2 wk.	Retropharyngeal abscess	15	15	394	78.5	200	50	0.5 Cu + 1 Al	Papillary carcinoma thyroid
851	M, W	10 yr.	Hearing loss; Rx to nasopharynx	21	11	1,770	?	145	50	0.25 Cu + 1 Al	Papillary carcinoma thyroid
1,133	M, N	7 yr.	Acute parotitis	21	14	1,350	20	140	40	4 Al	Papillary cystadenocarcinoma thyroid
1,041	M, W	1 mo./ 7 yr.	Thymus Tinea capitis	10	10 3	315 330	20 + epil.	140	40	4 Al	Carcinoma thyroid
1,337	M, W	1 yr.	Cervical adenitis	10	9	350	28	140	40	4 Al	Carcinoma thyroid
1,504	M, W	<1 yr.	Thymus	23	23	?	?	?	?	?	Carcinoma thyroid
385*	F, W	7 mo.	Thymus	21	21	?	?	?	?	?	Carcinoma thyroid
		14 yr.	Pansinusitis	21	7	490	49	140	40	0.25 Cu + 1 Al	
1,027	F, W	1 yr.	Adenoiditis	8	7	600	78.5	140	50	0.25 Cu + 1 Al	Mucoepidermal carcinoma rt. parotid
1,217	M, W	11 yr.	Cervical adenitis	22	11	400	225	200	50	0.5 Cu + 1 Al	Glioblastoma multiforme brain
819	M, W	7 yr.	Cervical adenitis	18	11	450	225	200	50	0.5 Cu + 1 Al	Adenocarcinoma submaxillary gland
338	F, W	12 yr.	Deafness	30	18	1,020	20	145	50	0.25 Cu + 1 Al	Carcinoma rt. breast
385*	M, W	2.5 mo.	Thymus	19	19	?	?	120	?	4 Al	Squamous-cell carcinoma nasal vestibule
515	M, W	1 mo.	Thymus	4	4	?	?	100	?	0.25 Cu + 1 Al	Leukemia
676	F, W	13 yr.	Cervical adenitis	13	0	100	?	100	25	4 Al	Malignant teratoma ovary

* Brother and sister (see also case 385, Table VIII).

TABLE IX: PATIENTS WITH BENIGN NEOPLASMS FOLLOWING IRRADIATION

Family Index No.	Sex and Race	Age at Time of Therapy	Reason for Therapy	Age at Diagnosis of Neoplasm (years)	Interval Between Irradiationand Diagnosis (years)	Dose (r in air)	Field Size (sq. cm.)	Kilovoltage (kvp)	Target-Skin Distance (cm.)	Filtration (mm.)	Types of Neoplasm
Thyroid											
295	M, W	2 yr.	Cervical adenitis	18	16	510	78.5	145	50	0.25 Cu + 1 Al	Papillary cystadenoma thyroid
355	M, W	5 mo.	Thymus	8	8	75	78.5	200	50	0.5 Cu + 1 Al	Follicular adenoma thyroid
481	F, W	4 days	Thymus	21	21	?	?	100	50	0.25 Cu + 1 Al	Fetal adenoma
654	F, W	1 mo.	Thymus	25	25	?	?	130	?	4 Al	Follicular adenoma thyroid
1,336	F, W	1 yr.	Cervical adenitis	19	18	216	78.5	200	50	0.5 Cu + 1 Al	Fetal adenoma
1,378	F, W	5 yr.	Cervical adenitis	18	13	800	78.5	200	50	0.5 Cu + 1 Al	Fetal adenoma
447	F, W	2 yr.	Cervical adenitis, peritonsillar abscess	17	15	320	78.5	200	50	0.5 Cu + 1 Al	Neurofibroma larynx
Osteochondroma											
129	F, W	2 yr.	Hypertrophic tonsils and adenoids	10	8	750	50	120	40	3 Al	Rt. tibia
626	M, W	3 mo.	Cervical adenitis	17	17	450	38.5	150	40	4 Al	Humerus
683	M, W	1 wk.	Thymus	16	16	150	?	140	50	0.5 Cu + 1 Al	Humerus
Breast											
504	F, W	2 mo.	Thymus	20	20	342	78.5	100	50	1 Al	Fibroadenoma
764	F, W	2 days	Thymus	19	19	?	?	100	?	0.25 Cu + 1 Al	Fibroadenoma
1,163	F, W	3 wk.	Thymus	18	18	125	78.5	130	30	?	Fibroadenoma
1,389	F, W	13 yr.	Pneumonia	23	10	500	225	200	50	Thoraeus	Intraductal papilloma
242	F, W	5 yr.	Cervical adenitis	16	11	510	78.5	200	50	0.5 Cu + 1 Al	Fibroadenoma
Other Neoplasms											
849	M, W	2 days	Thymus	3	3	100	78.5	140	50	0.25 Cu + 1 Al	Hemangioma thigh
1,124	F, W	1 wk.	Thymus	14	14	?	38.5	110	?	0.25 Cu + 1 Al	Multiple pigmented nevi
454	M, W	9 yr.	Pneumonia	13	4	364	78.5	200	50	0.5 Cu + 1 Al	Osteoclastoma rt. tibia

1 intraductal papilloma. There was 1 osteoclastoma of the tibia, 1 hemangioma of the thigh, and 1 case of multiple pigmented nevi. The various benign neoplasms of the siblings are shown in Table X. There were no thyroid adenomas and no osteochondromas in this group.

Although there are few data on the normal incidence of thyroid adenoma, the occurrence of 5 adenomas in Simpson, Hempelmann, and Fuller's (19) series agrees closely with 7 in our series. In Moloney's material, as reported by Snegireff (20) and subsequently by Moloney (14), the incidence of thyroid adenoma appears disproportionately high. Simpson *et al.* have commented on the increase in the number of osteochondromas in their patients. There were 3 osteochondromas in our series, of which 2 were in the upper extremity. The possibility that the 5 benign breast tumors could have been influenced etiologically by the radiation should also be considered.

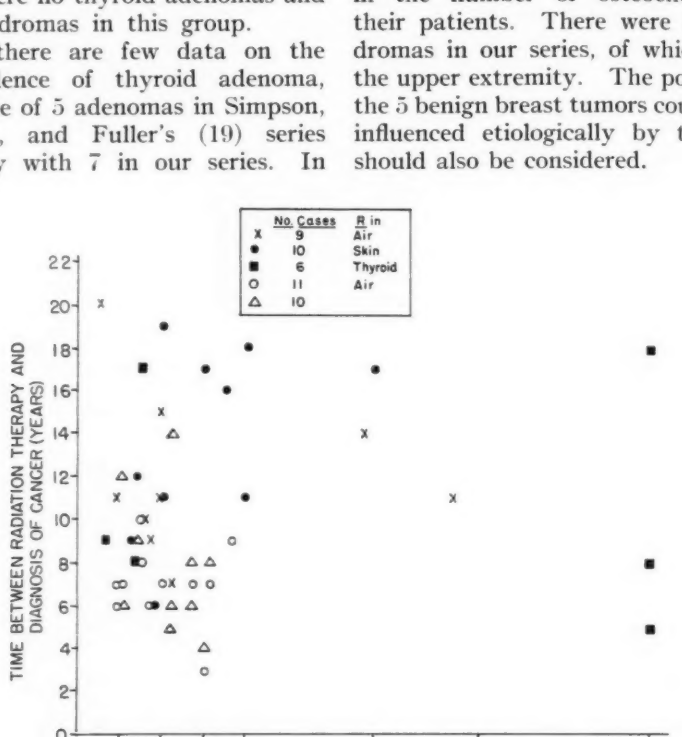

Fig. 3. Relation of x-ray dose to time between radiation therapy and diagnosis of carcinoma of thyroid in 58 patients. X Our series; ● Simpson and Hempelmann (18); ■ Wilson et al. (23); ○ Clark (3); △ Majarakis, Slaughter and Cole (13).

TABLE X: NONIRRADIATED SIBLINGS (CONTROLS) WITH BENIGN NEOPLASMS

Family Index No.	Sex and Race	Age at Diagnosis (years)	Neoplasm
226	M, W	Birth	Capillary hemangioma, left upper extremity
411	F, W	20	Adenoma breast
454	M, W	1	Hemangioma skin
527	F, W	28	Fibroadenoma breast
567	F, N	27	Neurilemmoma
978	F, W	14	Epidermal nevi
943	M, W	1	Hemangioma
1,243	F, W	25	Adenoma breast

One might assume that there would be a simple relation between dose delivered and the latent period between treatment and detection of neoplasm. In a review of 58 cases from several studies including our own (3, 7, 13, 18, 23), no such simple relation was found. Figure 3 shows a scatter plot of these data. The latent period for doses between 100 and 800 r ranges from three to twenty years.

The relation of field size to induction of thyroid neoplasms needs also be considered. Figure 4 shows the relation of

several field sizes to the thyroid in infants and Figure 5 shows the same relations for a six-year-old child. Again no simple relationship between field size and induction of neoplasm was found, although field sizes in the cancer patients in this study were 38.5 to 225 sq. cm., being considerably larger than the 16-sq. cm. field used in the patients reported by Conti *et al.* (4).

Morbidity: A number of "detractor" questions were put into the interview primarily to avoid recognition by the

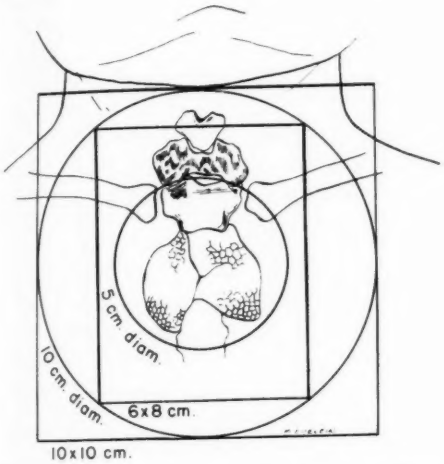

Fig. 4. Areas covered by various treatment fields centered over the thymus gland of an infant.

informant of the true purpose of the survey. This step was decided upon to eliminate bias in replies as well as to avoid fear on the part of those interviewed. These detractor questions have proved interesting in themselves. Since Berkson (1) has pointed forcefully to possible and unsuspected effects of selecting special populations for cancer studies it was felt desirable to analyze the data dealing with general morbidity and mortality.

It was found that the patients tended to have a higher incidence of every disease than their sibling controls. For clearer presentation, each observed disease incidence was adjusted for life-years contributed by sex, age, and race. The resulting disease rates and the ratio of patient to sibling disease rate are given in

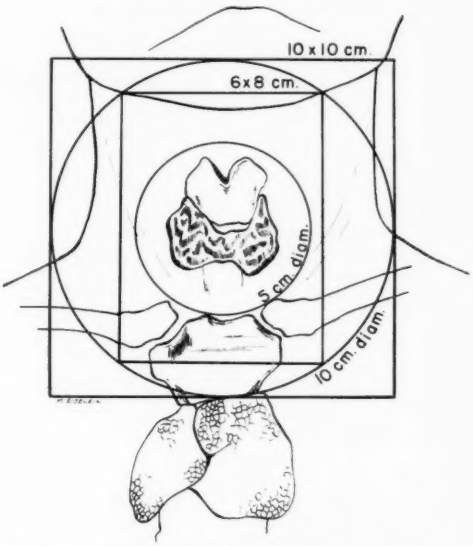

Fig. 5. Areas covered by various treatment fields centered over the neck of a six-year-old child.

TABLE XI: RATIOS OF PATIENT/SIBLING INCIDENCE OF DISABLING DISEASES
(Adjusted for Contributing Life-Years)

Category of Disabling Diseases	Siblings per 100,000	Patients per 100,000	Patients/ Siblings
Circulatory diseases	21.9	115.5	5.27
Malignant neoplasms	16.1	59.4	3.7
Respiratory diseases	31.1	115.5	3.59
Nervous diseases	29.2	95.7	3.28
Blood and blood-forming diseases	10.2	33.0	3.23
Mental diseases	30.6	82.5	2.69
Infections	17.5	42.9	2.44
Genitourinary diseases	24.8	46.2	1.86
Digestive diseases	19.0	23.1	1.22
Allergic, endocrine, metabolic, and nutritional diseases	93.4	99.0	1.06

Mean ratio 2.74 ± 1.31.

Table XI. The diseases for which rates and ratios are given in that table are those on account of which individuals either were incapacitated or demanded constant medical or other care. With due acknowledgment of the many sources of error contained in recollection of past morbidity, it seems reasonable that errors of over, under, or misreporting would occur with equal frequencies for patients and siblings, especially since the informant had no way of telling these two groups apart.

TABLE XII: OBSERVED *vs.* EXPECTED DEATHS* AMONG PATIENTS
(This table is based on 1,644 subjects)

Age Distribution	Contributing Life-Years	Observed Deaths	Expected Deaths (U. S. Rates)	Expected Deaths (Ohio Rates)
Under 1 year	754	9	19.19	17.64
1–4	6,575	4	9.23	8.67
5–14	14,803	6	9.23	9.01
15–24	6,468	7	8.45	8.26
25–34	754	0	1.36	1.27
35–44	10	0	0.03	0.03
TOTALS	29,364	26	47.49	44.88

* Expectation based on death rate for United States and State of Ohio as given in Vital Statistics-Special Reports 49, 1958. U. S. Department of Health, Education and Welfare.

TABLE XIII: OBSERVED *vs.* EXPECTED DEATHS* AMONG SIBLINGS
(This table is based on 3,777 subjects)

Age Distribution	Contributing Life-Years	Observed Deaths	Expected Deaths (U. S. Rates)	Expected Deaths (Ohio Rates)
Under 1 year	3,702	139	126.59	116.82
1–4	14,296	54	20.46	19.09
5–14	28,933	25	17.85	17.38
15–24	15,564	21	20.18	19.46
25–34	5,030	7	9.32	8.68
35–44	741	2	2.73	2.72
45–54	52	0	0.46	0.46
55–64	1	1	0.00	0.00
TOTALS	68,319	249	197.59	184.61

* Expectation based on death rate for United States and State of Ohio as given in Vital Statistics-Special Reports 49, 1958. U. S. Department of Health, Education and Welfare.

Comparing the incidence of disabling diseases for patients and their sibling controls, one can see that the former appear to have an affinity for all diseases, a tendency that seems to be considerably greater than that of their controls. Compared to their controls, patients show a fivefold increase in circulatory diseases, a threefold increase in at least three disease categories (respiratory, nervous, and blood-forming organs), and a smaller but consistent increase for all other illnesses.

There is some question of just how the relative cancer rates fit into this picture. If all the malignant lesions reported and verified are considered, one finds that the 11 cases for siblings and the 18 cases for patients yield a ratio of 3.7. This is close to the mean patient/sibling ratio of 2.74 (S. D. = 1.31) for all diseases, considerably lower than the ratio for circulatory diseases, and about equal to the ratios of respiratory and nervous diseases and diseases of blood and blood-forming organs.

TABLE XIV: DIFFERENCES BETWEEN OBSERVED AND EXPECTED DEATHS FOR PATIENTS AND SIBLINGS

Age	Difference: Observed − Expected Deaths	
	Patients	Siblings
<1	−10.19	+12.41
1–4	−5.23	+33.54
5–14	−3.23	+7.15
15–24	−1.45	+0.82
25–34	0	0
35–44	0	0
	−20.10	+53.92

If patients with malignant disease who are over the age of twenty-three are removed from the sample, the ratio is raised to 8.5 and becomes the highest for the group of diseases studied. This latter ratio of 8.5, however, is not comparable to the others, since patients over twenty-three were not removed from other disease categories.

It appears then that patients average about 2.74 times the incidence of disabling diseases as do their controls. This finding points to a possible selection factor, which was explored further by comparing death rates for the two groups.

Mortality: The numbers of deaths of patients and siblings are detailed in Tables XII and XIII. The contributing person-life years were calculated for each group. The figures for expected deaths according to U. S. and Ohio rates were corrected for sex and race distributions of the observed sample (see Appendix). The differences in observed *versus* expected deaths for the patients and siblings are shown in Table XIV. The minus values are the decrease in expected deaths for patients; the plus values are the increase in deaths for siblings. Thus, in our population patient deaths are lower than expected and sibling deaths higher than expected.

Several interesting observations have emerged from the mortality aspects of our

TABLE XV: COMPARISON OF PROSPECTIVE STUDIES OF THYROID AND OTHER NEOPLASMS

Study	Cancer Thyroid Pts/ Sibs	Adenoma Thyroid Pts/ Sibs	Leukemia, Lymphoma Pts/ Sibs	Other Cancers Pts/ Sibs	Dose Range (r)	Latent Period for Thyroid Carcinoma	Total Patients Irradiated	Controls	Incidence Thyroid Carcinoma per 100,000 in Patients	Remarks
Conti *et al.*	0/0	0/0	0/3	0/0	75–200 1,386 pts.; 200–450 178 pts.	0	1,564	2,923	0	Small ports. Nearly random sample
Simpson and Hempelmann	11/0	5/0	7/0	3/0	<200; >600	6–19 yr.	1,502	1,933	732	Larger ports. Selected population
Latourette and Hodges	1	0	2	1	50–600	9 yr.	867	0	115	Selected population
Saegireff	2*/0	5/0	0/0	0/0	100–1800 mean 400	?	148 (125*)	162+ 23	1,600*	Selected population
Saenger, Silverman, Sterling, and Turner	11/0	7	1/3	6	50–1200+	7–23 yr.	1,644	3,777	669	Selected population

* See reference 14.

study. The first was that the death rate of the siblings was rather high. This fact was particularly clear in the sibling group under one year and in that from one to four years. Under one year there were 139 deaths observed as compared to an expected number of 126.59 calculated by U. S. vital statistics rates, and 116.88 as calculated on the basis of death rates for the state of Ohio. In the group one to four years there were 54 deaths as compared to 20.46 for the United States and 19.09 for Ohio. The deaths between five and fourteen years numbered 25 as compared to expectations of 17.85 and 17.38 respectively. Subsequent deaths were approximately as expected. The total number of deaths in the sibling group is 249. But in the patient group there were only 26 deaths in the entire group as compared to 47 expected deaths for the United States and 45 for Ohio.

The tables of expected differences between actually observed deaths and death expectancies based on United States and Ohio age-specific rates were tested for statistical significance in two ways. First, a test was performed on the hypothesis that the observed deaths were a chance departure from expected deaths. Because of the small frequencies in some of the cells, it was necessary to combine expectancies and observations for some of the life years. For the siblings, the distribution was tested for life years under one year of age, one to four years, five to fourteen, and fifteen and over; for the patients under one year and one year and over. In both cases χ^2 was highly significant, being 61.22 with 3 degrees of freedom ($p < 0.001$) for siblings and 9.01 with 1 degree of freedom for the patients ($p < 0.01$). In addition, the hypothesis was tested that the two distributions, of observed deaths and expected deaths of siblings, were stochastically of equal size. Essentially this test would determine whether the siblings die earlier than expected. The test itself is derived from the Kolmogorov-Smirnov two-sample test (10). For the siblings the probability that the death distribution is not stochastically smaller is less than 0.02. From this analysis one can infer that deaths occur earlier in this group than expected. In both cases the comparisons were made between observed deaths and death expectations based on the United States rates. This technic is perhaps weaker and more conservative, since the differences were more pronounced for the death expectancies based on the Ohio death rate.

DISCUSSION

Four prospective studies concerned with the incidence of neoplasia following irradiation in children have been reported in recent years. Table XV compares the findings in these several surveys with ours. Conti, Patton, Conti, and Hempelmann (4) reported findings in a group of 1,564 children given x-ray treatment to the thymus gland between 1938 and 1946. Two hundred and twenty-four children were treated because of the radiological diagnosis of enlarged thymus, although for the most part they were asymptomatic. Eighty per cent of this subgroup received 200 to 450 r to the anterior mediastinum. The remainder were given a somewhat lower dose. Subsequently all children (1,340) born between June 1944 and May 1946 received x-ray therapy to the manubrial region. Ninety-five per cent of the 1,340 children so treated were given 150 r, and the remainder 75 to 100 r. Therapy was given with 140 kvp, 3 mm. Al filtration, and a port size of 16 sq. cm. over the manubrium. No cases of thyroid cancer or leukemia were found in the treated patients when the families were contacted between 1956 and 1958. There were 4 cancers including 1 leukemia and 2 lymphomas in a group of 2,923 untreated siblings.

On the other hand, the study of Simpson and Hempelmann revealed 11 cancers of the thyroid in a group of 1,502 irradiated patients. The technic of their study was similar to ours in that the sample at risk was one which was referred for irradiation because of actual or suspected disease rather than one which was asymptomatic. The increase in the number of patients with cancer of the thyroid as compared with unirradiated siblings was highly significant, as was the increase in the number of leukemias. Latourette and Hodges (12) reported 1 cancer of the thyroid in a group of 867 patients.

Snegireff (20), in a paper entitled "The Elusiveness of Neoplasia Following Roentgen Therapy for Thymic Enlargement in Childhood," reported no malignant changes in a group of 148 persons who received roentgen irradiation in childhood and infancy because of an enlarged thymus gland. Reference is made in this paper to a group of 99 patients studied by Dr. W. C. Moloney at Boston City Hospital. Snegireff states that of the 7 dead in this group of 99, only 2 had neoplasia possibly attributable to radiation exposure. Subsequently Moloney (14) stated that, in the expansion of this group to 125 patients, 2 carcinomas and 5 adenomas of the thyroid were discovered. While the selection procedure followed by Snegireff appears to be similar to the one used by Simpson and Hempelmann and to that used in the present study, the number of cases in his population is too small for any valid conclusions, especially when compared to Moloney's data.

Several investigators have stated with regret that the ideal control series of children is not available and probably cannot become available. This so-called ideal control group would be a group of children with enlarged thymus who did not receive irradiation. It is our opinion, however, that any normal group of children would constitute an ideal control. We have already alluded to the inadequacies in the radiologic diagnosis of enlarged thymus. If we accept the work of Hammar and Boyd, we must also accept the concept that the thymus is normally large in comparison with the so-called normal standard used for evaluation of the treated children. On this basis, it would not seem necessary to search any further for the ideal group but to accept the control groups already described as adequate, with reservations only in so far as selection for factors other than enlarged thymus is concerned.

It is then interesting to note that the two investigations which employ very similar technics of selection report almost identical findings, while the one study that concentrated on routine irradiation found no cases at all. It appears reasonable to accept the proposition that the referred patients have, as their reference

population, individuals who differ from the "norm" by the tendency toward diseases in general.

One aspect of this study is its ability to raise questions rather than to answer them. What about the increase in general morbidity in the group of patients? Is one to suppose that this too is an effect of radiation? If this hypothesis be accepted, one is faced with the decline in patient deaths. Is that also to be considered a by-product of radiation treatment? Clearly, one cannot assert the former without commitment to the latter, and conversely.

One alternative appears reasonable here, namely, that the method of selecting patients has introduced the investigator to a special set of individuals who suffer from a variety of diseases to a much greater extent than do others. The experience of irradiation itself may have been the consequence of disease rather than its precursor. Thus the patient was referred for treatment because he was ill and did not become ill because he underwent treatment. This possibility, besides being reasonable, is supported by the similarity of results in this study and in the study of Simpson *et al.* In both instances the index cases involved children who were referred for irradiation specifically; apparently there was sufficient deviation from "normal" to lead the physician to undertake diagnostic procedures and ultimately to recommend radiation therapy. This explanation also fits the deviations of the mortality data. The excess deaths among the siblings during their early ages may have been among individuals who were destined to become patients but died before coming to the attention of the radiologist. Only the more viable of these potential patients survived to become patients in fact. It is interesting to note that of the observed sibling deaths, 60 occurred on the first day of life and 75 during the first week.

One may now comment on the relation between radiation and thyroid cancer in this apparently selected population. It remains a fact, indisputable in all respects, that the rate of thyroid cancers in the irradiated group is disproportionately high. Not even reference to special differences for the selected population of patients can illuminate why a concentration of carcinomas occurs in the area sharply circumscribed by radiation therapy.

Three possible explanations may be advanced:

1. Irradiation of the thymic region is a cause of thyroid cancer: In view of the Conti study, one is forced to reject this alternative.
2. The observed relation between thymic irradiation and increased incidence of thyroid cancer is spurious, due to the fact that a highly selected population has been studied: Until further study or until one finds a larger incidence of thyroid cancer cases among relevant siblings, such an alternative must be rejected. The differences between expectations and observations are simply too large to be shrugged off as being entirely due to sampling error. Also, the differences in incidence here are out of proportion to what may be expected from other comparisons between patient and control populations. It is possible that the search for thyroid cancer was not as intense among controls as it was among patients in this and other studies. However, the controls are individuals who also have fewer contacts with hospital records and it may be that further discoveries of cases among siblings will make this alternative more attractive. Until such time, this hypothesis remains unacceptable despite the latter considerations.
3. Irradiation of the thymic region is a contributing cause to the occurrence of thyroid cancer in some individuals. Past and present evidence makes this a very attractive explanation. To some extent it is also a

troublesome notion. If the evidence presented here supports the deleterious effects of radiation, it also supports a possible decrease in mortality. The physician must certainly consider both possibilities in evaluating radiation treatment for a child whom he may suspect of belonging to a population of children prone to disease in general.

From the point of view of the radiation therapist, much helpful information can be derived from these studies. The prospective studies on selected children referred because of sickness and irradiated with portals of 20 to 100 sq. cm. have shown an increase of thyroid neoplasia about one hundred times that expected by chance alone. Apparently there was no specific shielding of the thyroid gland in these patients.

In the future, certain benign conditions will probably continue to require radiation treatment. These conditions include infection and/or hypertrophy of tonsils and adenoids and lymphoid hyperplasia of the fossa of Rosenmueller and benign neoplasms, as hemangiomas and lymphangiomas. With a definite and serious increase in the prevalence of drug-resistant microorganisms, it may again be necessary to resort to radiation therapy to prevent increased morbidity and perhaps even death in certain infections about the head, neck, and chest. If such treatment is employed, one must then review the technic of administration so as to minimize the danger of induction of neoplasia. In treating infection during past years, at Children's and General Hospitals in Cincinnati, relatively large portals have been utilized so as to include all possible diseased tissue. It now appears desirable to make these ports as small as possible and also to shield the thyroid gland to reduce its dose from roentgen to milliroentgen levels. Most acute infections seem to respond to dose increments of 25 to 50 r as well as to larger increments of 100 to 200 r. Thus, by careful clinical observations, a total dose of 100 to 150 r over two to five days may be achieved rather than doses of 300 to 500 r. The use of lead blocks in addition to light-centering therapy cones will minimize the effect of penumbra, particularly with long target-skin distances and in the event of malalignment of the coning device. Thus the therapist can be reassured of the safety of the child if treatment is indicated for nonmalignant disease.

The radiation therapist should not feel a sense of reticence or reluctance in employing this modality when indications exist. The concept of the enlarged or abnormal thymus has now been abandoned. In our series, about 44 per cent of the patients were treated for serious infections for which no other specific therapy was then available and thus no alternative treatment could be used. To the degree that such indications for treatment exist today or in the future, either for infections or benign tumors, appropriate therapy should be vigorously and adequately pursued.

SUMMARY AND CONCLUSIONS

1. A series of 1,644 persons of a total of 2,230 who were irradiated over the head, neck, and chest in infancy and childhood were compared with 3,777 siblings with respect to subsequent medical history.

2. Eleven carcinomas of the thyroid were found in the patient group; none were found in the sibling controls. This incidence of carcinoma of the thyroid in the irradiated group is about one-hundred times that expected from current tables of morbidity and is comparable to that reported in other similar surveys.

3. The incidence of infections and other non-neoplastic illness was greater among the patients than among their siblings. But a statistically significant difference in the mortality ratio in the two groups was also found, *i.e.*, the death rate in the siblings was greater than that in the patients.

4. Although there is a significant in-

crease in the incidence of cancer of the thyroid following irradiation, radiation does not appear to be the sole factor responsible for the increased incidence but rather a contributing factor.

5. This survey differs from previously reported surveys in the extent to which the total family health history was evaluated. The information obtained is extremely useful in placing in proper perspective possible carcinogenic factors other than radiation.

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APPENDIX

In computing person-life years, patients cannot be considered to have been at risk during the time elapsed between birth and radiation treatment. The count of person-years started the month following treatment.

U. S. and Ohio death rates were adjusted for a population with sex and race distribution like that of the patient and sibling groups; separate expected rates were obtained for each group. Expected deaths were computed for each age group separately, and the results summed in the usual manner.

It can be argued that a subject who falls into the category of a patient had to survive at least until the moment of irradiation before he could be a subject in this study. One cannot, therefore, consider an individual in the patient group at risk until after he has undergone the treatment which selected him as a subject. In computing contributed person-years the years prior to treatment were therefore subtracted from the life years contributed by each patient. For instance, in Table XII the total number of life-years contributed for one year or under equals 754, although 1,644 patient subjects survived the first year of life. Another adjustment was made in the computation of comparable risks for Ohio and U. S. populations. Published rates for total populations (*i.e.*, including both male and female and all races) are computed on the basis of the population enumerated as of April 1, 1950. In the present sample, the number of males and females, whites and nonwhites, may not correspond to this distribution (Table II). The death rates expected for each age group were corrected for the proportion of male and female, white and nonwhite life-years contributed by the different population categories in the sample. The final rates differ therefore by some small margins from figures published in the U. S. Vital Statistics, Special Report 49 1958, although these rates are based on figures reported there.

The first year death rate for the patients was further modified. The first two weeks of life contribute heavily to first year mortality. It would not be proper to apply first year mortality rates, even to the reduced number of patient-years at risk. First year death rates, therefore, were adjusted for mortality during the first two weeks of life.

It should be noted that the uses of 1949 to 1951 mortality statistics represent a bias within themselves. Risks during years of many actual deaths were higher than in 1949 to 1951. The expected number of deaths should be higher by some small unknown factor for both sibling and patient groups. The given estimates, faulty as they may be, were deemed to be sufficient for present purposes.

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SUMMARIO IN INTERLINGUA

Neoplasia post Irradiation Therapeutic pro Benigne Conditiones in Juveniles

Un serie de 1.644 subjectos—ex un total de 2.230 subjicite al etate juvenil a irradiation therapeutic in capite, collo, e thorace—esseva comparate con 3.777 fraternos ab le puncto de vista de lor subsequente historial medical.

Dece-un carcinomas del thyroide esseva trovate in le gruppo de patientes; nulle esseva trovate in le gruppo de controlo del fraternos. Iste incidentia de carcinoma del thyroide in le gruppo irradiate es circa cento vices plus alte que lo que pote esser expectate secundo le currente tabulas de morbiditate. Illo es comparabile al resultatos reportate pro altere simile investigationes.

Le incidentia de infectiones e de altere morbos non-neoplastic esseva plus alte inter le patientes que inter lor fraternos. Sed etiam un statisticamente significative differentia del mortalitate esseva trovate inter le duo gruppos: Le mortalitate inter le fraternos del patientes esseva plus alte que inter le patientes mesme.

Ben que il existe un augmento significative del incidentia de cancere del thyroide post irradiation, il non pare que le irradiation es le sol factor responsabile pro le augmentate incidentia; illo es plus tosto un factor contributori.

Le presente investigation differe ab previemente reportate investigationes del problema per le grado a que le historia medical del familias total esseva evalutate. Le informationes colligite es extrememente utile in le obtention de un juste perspectiva de possibile factores carcinogenic altere que le radiation.

Radiation and Leukemia in Carcinoma of the Cervix

NORMAN SIMON, M.D., MARSHALL BRUCER, M.D., and RAYMOND HAYES, Ph.D.

THERE IS STILL considerable concern over radiation leukemogenesis on the part of physicians as well as laymen. For this reason we have studied the incidence of leukemia in patients with cancer of the cervix who have survived after radium treatment.

Cancer of the uterine cervix was selected because it is a common tumor and there are many survivors. In those countries where statistics on the incidence of disease are kept, cervical cancer is known to have a high incidence, ranking after cancer of the digestive tract and of the breast. Survival data for this neoplasm have been studied for many years, and have been published in the *Annual Report on the Treatment in Carcinoma of the Uterus* (1, 2). No other form of cancer treated with radiation has such precise documentation. It is the only medical situation in which there may be enough cases to establish statistical significance (3). In general, about 40 per cent of the patients survive five years and about 75 per cent survive one year.

The radium dosage has been practically uniform. It has been common practice for almost fifty years to insert a radium tube (tandem) into the uterus and an applicator (colpostat) into the vagina, exposing the patient to 5,000 to 9,000 mg. hr. In the lower stages of disease the prognosis is good, and the survival rate is high. Advanced cases (Stages III and IV) have a low survival rate. Patients with advanced carcinoma of the cervix (Stages III and IV) are less likely to have been treated with radium than the more favorable groups comprising Stages I and II. It may then be assumed that those patients treated with radium have even higher survival rates than are reported for cancer of the cervix as a whole, including all stages. The disease occurs among relatively young women, which contributes to the comparatively high survival. It may be assumed that patients who have been treated with radium have been exposed to about 8,000 mg. hr. in the pelvis in thirty days or less.

In this study we have collected data both as to the number of survivors of radium treatment for cancer of the cervix and the number of cases of leukemia occurring in these survivors. Many of the patients received external irradiation with x-rays to increase the dose of radiation to the lymph node areas in the pelvis. This added radiation results in a dose of 2,000 to 3,000 rads throughout the pelvis, including a large part of the pelvic bones. The heads and necks of the femurs are also included. Some institutions omit this external irradiation in Stage I cases, but the vast majority of the survivors have received this additional therapy.

The amount of bone marrow receiving radiation is probably an essential feature of both this series and the rheumatoid spondylitis series of Court-Brown (4, 5, 6). The volume of bone marrow irradiated in cancer of the cervix is greater than the volume of bone marrow irradiated in rheumatoid spondylitis, but the distribution of the dose is considerably different. There is no way of estimating accurately the administered dose in the rheumatoid spondylitis patients of Court-Brown just as there is no way of estimating accurately the dose administered to bone marrow from the external irradiation in this study. For this reason, we have omitted external irradiation from direct consideration. However, we can reach a reasonable estimate of dose delivered to bone marrow

[1] From the Medical Division, Oak Ridge Institute of Nuclear Studies (N. S., Consultant; M. B., Chairman; R. H., Chemist), Oak Ridge, Tennessee, under contract with the United States Atomic Energy Commission. Presented at the Forty-fifth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov. 15–20 1959.

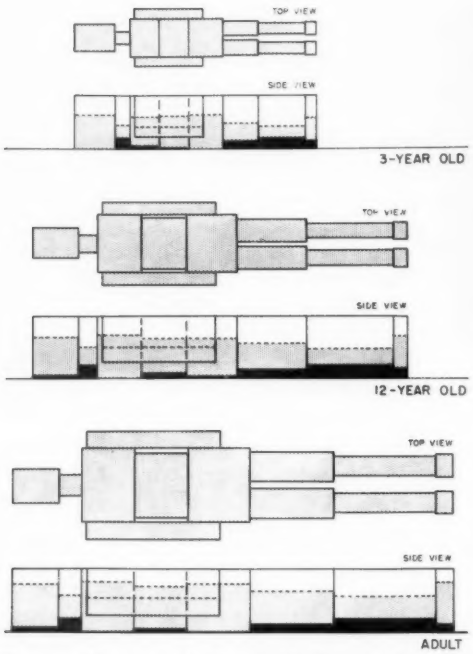

Fig. 1. Diagrams of the standard-man phantoms.

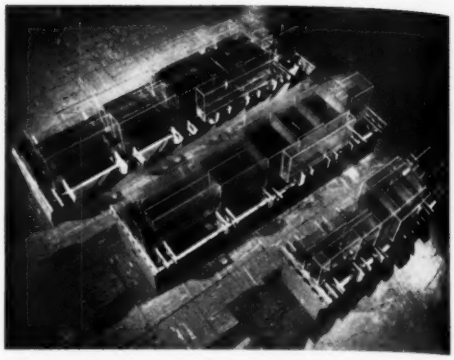

Fig. 2. Photograph of the standard-man phantoms.

from the radium used in cancer of the cervix. With the aid of a series of body phantoms composed of water-filled compartments, we have made measurements of the dose absorbed by patients receiving a "cervix" system of 8,000 mg. hr.

Figures 1 and 2 show the phantoms used in this study. They are multipurpose phantoms designed to simulate a standard adult, an adolescent (twelve years old), and a child (three years old). The design of each is based on pertinent anthropometric measurements available in the literature (7). When filled with water to the levels indicated in Figure 1, these compartmentalized phantoms are reasonable approximations of the male human body. For the purposes of this estimation of dose, we believe that these particular phantoms also represent a reasonable approximation of the female human body.

Dose measurements on the three phantoms were made as follows: The phantoms were filled with water and four large sources of encapsulated radium (200 mg. each) were positioned in the pelvic compartment to simulate the tandem and colpostat arrangement normally used in the treatment of carcinoma of the cervix. Thimble-chamber measurements in the compartments outside the pelvis were made on each phantom. The figures obtained were then converted to rads with the aid of a series of ferrous sulfate chemical dosimetric measurements made on the adolescent phantom. This procedure necessarily assumes energy independence for the yield (G factor) of the ferrous system.

Figure 3 shows the results of this study. The dose measurements for the adult and child phantoms have been normalized to the dimensions of the adolescent phantom compartments to aid the comparison. The adolescent is assumed to be approximately equivalent in size to the "average" woman and the adult and child phantoms to "large" and "very small" women, respectively. Figure 4 shows a different treatment of the data. Average compartment doses obtained by graphical integration are plotted against the overall height of the phantoms.

Both Figure 3 and Figure 4 serve to emphasize the large effects that variations in body height produce on the absorbed dose outside the pelvic compartment. Admittedly these measurements involve a number of assumptions. The study was not intended, however, to be a definitive one but rather to act as a guide in interpreting the results of the survey that was planned.

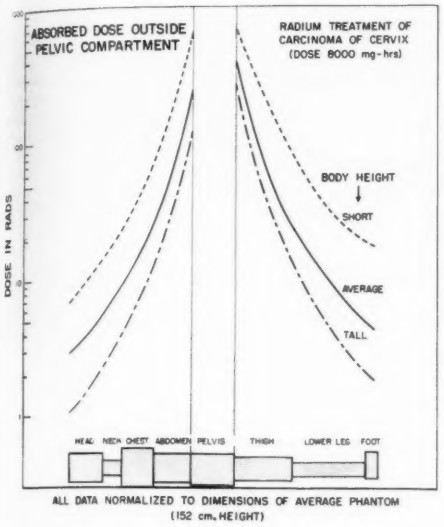
ABSORBED DOSE OUTSIDE PELVIC COMPARTMENT
RADIUM TREATMENT OF CARCINOMA OF CERVIX (DOSE 8000 mg-hrs)
BODY HEIGHT
SHORT
AVERAGE
TALL
DOSE IN RADS
HEAD NECK CHEST ABDOMEN PELVIS THIGH LOWER LEG FOOT
ALL DATA NORMALIZED TO DIMENSIONS OF AVERAGE PHANTOM (152 cm. HEIGHT)

Figure 3.

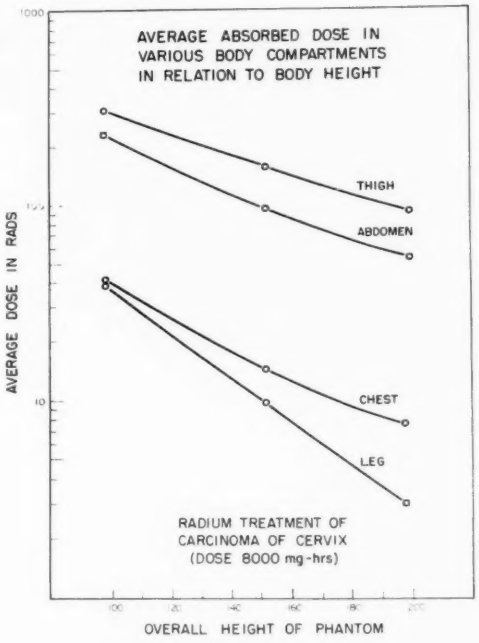
AVERAGE ABSORBED DOSE IN VARIOUS BODY COMPARTMENTS IN RELATION TO BODY HEIGHT
THIGH
ABDOMEN
CHEST
LEG
AVERAGE DOSE IN RADS
RADIUM TREATMENT OF CARCINOMA OF CERVIX (DOSE 8000 mg-hrs)
OVERALL HEIGHT OF PHANTOM

Figure 4.

What we can say from this series of measurements is that, when a patient is treated with radium with a "standard" technic, thousands of rads will be delivered to the bone marrow of the pelvis; hundreds of rads will be delivered to the bone marrow of the thighs and abdomen; tens of rads will be delivered to the bone marrow of the thorax and legs; and a few rads will be delivered to the bone marrow of the head and the feet.

This radiation is delivered in approximately thirty days. This is one kind of radiation exposure that might or might not be leukemogenic. It is not the same as the radiation in the treatment of ankylosing spondylitis, nor is it likely to be exactly the same as any other kind of radiation treatment. If, however, radiation *per se* is leukemogenic, then we have here a large dose delivered to a large volume of bone marrow. Also, this is the one disease in which we have a sufficiently large experience so that a survey of results should be of value.

THE SURVEY

To collect a large number of cases of cancer of the cervix with survival the cooperation of many large treatment centers was solicited by mail, and some were visited personally. The contributors (see Table I) were those who had been submitting their statistical data to the *Annual Report on the Results of Treatment in Cancer of the Uterus* (1).

A letter was sent to collaborators in Volume 11 of the *Annual Report* published in 1958, asking that they supply the following data:

1. The number of patients with carcinoma of the cervix treated with radium.
2. The number of patients in this treated group in whom leukemia developed.
3. Details of each case of leukemia, including the type and the period of time between the radium treatment and the development of leukemia.

The responses of 36 collaborators yielded a total of 71,582 patients treated with radium for cancer of the cervix, with a crude total of 22 cases of leukemia.

TABLE I: COLLABORATORS IN PRESENT STUDY

Index No.	Collaborator	No. Ca. of Cervix Radium Treated	No. Leukemia	Our Case No.
1	A. V. Kozlova, Moscow Institute of Roentgenology and Radiology, Moscow, U. S. S. R.	8,117	1	1
2	G. Hilton, University College Hospital, London, England	554	0	..
3	Dr. Zeitz, Universitäts-Frauenklinik, Heidelberg, Germany	1,743	0	..
4	M. Dargent, Centre Léon Bérard, Lyon, France	1,045	1	2
5	A. A. Charteris, Western Infirmary, Glasgow, Scotland	523	0	..
6	C.-E. Johanson-Unnérus, University of Helsinki, Finland	158	0	..
7	H. R. Schinz, Zurich, Switzerland	96	0	..
8	J. Maisin, Cliniques Universitaires, Louvain, Belgium	1,988	0	..
9	J. S. Mitchell, University of Cambridge, Cambridge, England	199	0	..
10	M. H. Russell, Christie Hospital and Holt Radium Institute, Manchester, England	3,000	0	..
11	R. G. Maliphant, The Cardiff Royal Infirmary, Cardiff, Wales	2,000	0	..
12	J. S. Fulton, The Liverpool Radium Institute, Liverpool, England	2,758	0	..
13	H. W. Helbing, Thür. Universitäts-Kliniken, Jena, Germany	2,200	1	3
14	O. Dufresne, Institut du Radium, Montreal, Canada	1,667	0	..
15	C. Abernethy, St. Bartholomew's Hospital, London, England	224	0	..
16	M. D. Gilmour, The Marie Curie Hospital, London, England	2,640	2	4, 5
17	M. Lederman, The Royal Marsden Hospital, London, England	1,037	0	..
18	A. P. Lachapèle, Fondation Bergonié, Bordeaux, France	612	0	..
19	P. Lamarque, Centre Régional de Lutte Contre le Cancer, Montpellier, France	2,118	0	..
20	A. M. Evans, The British Columbia Cancer Institute, Vancouver, B. C., Canada	917	1	6
21	W. Bickenback, I. Frauenklinik und Hebammenschule, München, Germany	3,660	0	..
22	T. A. Watson, Saskatoon Cancer Clinic, Saskatoon, Saskatchewan, Canada	994	0	..
23	Z. Hlasivec, Onkologický Ústav, Praha, Czechoslovakia	1,600	1	7
24	R. Schröder, Universitäts-Frauenklinik Leipzig, Leipzig, Germany	2,012	0	..
25	M. Thiery, Verloskundige en Gynecologische Kliniek, Gent, Belgium	420	0	..
26	Dr. Halfpap, Universitäts-Frauenklinik, Göttingen, Germany	1,320	2	8, 9
27	J. P. A. Latour, Royal Victoria Hospital, Montreal, Canada	1,086	1	10
28	A. McKenzie, General Register Office, London, England	5,987	0	..
29	C. Krebs, University of Aarhus, Aarhus, Denmark	2,621	3	11, 12, 13
30	J. Nielsen, Finseninstitutet og Radiumstationen, Finsen Institute, Copenhagen, Denmark	6,141	2	14, 15
31	H.-L. Kottmeier, Karolinska Sjukhuset, Stockholm, Sweden	8,000	2	16, 17
32	R. C. Tudway, Bristol Royal Hospital, Bristol, England	2,250	1	20
33	J. Baud, Fondation Curie, Paris, France	4,059	1	18
34	S. Laborde, Institut Gustave Roussy, Paris, France	?	1	19
35	H. Schlink, Royal Prince Alfred Hospital, Sydney, Australia	1,426	0	..
36	I. H. Smith, Ontario Cancer Foundation, London, Ontario, Canada	693	1	21
37	K. Werner, Czerny-Krankenhaus, Heidelberg, Germany	397	1	22
38	A. N. Arneson, St. Louis, Missouri, U.S.A.	350	0	..

Analysis of the 22 cases of leukemia shows that in 6 patients the diagnosis was made simultaneously with the radium therapy or before its administration (Cases 3, 4, 5, 13, 16, and 22). Such cases cannot be attributed to radiation. Six instances of coincident leukemia in a population of more than 70,000 patients with carcinoma of the cervix is about the expected incidence (60 per million). This is in essential agreement with Sørensen (8), who found no great increase in multiple malignant disease in patients with cancer of the cervix.

Of the 16 cases of leukemia remaining after deduction of those occurring simultaneously with irradiation, one developed less than a year after irradiation, an interval too short for radiation leukemogenesis. Court-Brown and Doll, in their experience with leukemia after irradiation of ankylosing spondylitis (6), and Moloney, in his experience with atom bomb survivors (9), have been unable to establish a definite latent period between the time radiation is received and the development of leukemia. Court-Brown and Doll quote 2 cases appearing less than one year after irradiation, and Moloney indicates the lack of data for the first year or two after the bomb explosions in Japan. However, rather than argue about this 1 case

TABLE II: LEUKEMIA FOLLOWING IRRADIATION FOR CARCINOMA OF THE CERVIX

Of the total of 22 cases, 6 patients had leukemia before radium treatment was given (our case nos. 3, 4, 5, 13, 16, and 22), and these are to be deducted from the total of those whose disease could be induced by radiation. The remaining group of 16 patients with leukemia contains 4 with chronic lymphatic leukemia (our case nos. 7, 15, 17, and 18), a type which has been considered not to be due to radiation. There are left 12 patients whose leukemia could be associated with radiation.

Our Case No.	Type	Date of Radium Therapy	Date of Leukemia Diagnosis	Time Interval (years)	Age of Patient	Exposure Dose (mg. hr.)	Comments
1	?	?	?	2.5	?	900	.....
2	?	2-45	3-49	4	43	?	.....
3	?	Never	1952	..	?	0	Operation only, no radium
4	Acute	4-37	12-38	1.6	56	?	Patient alleged to have leukemia previously
5	Myeloid	5-53	5-53	0	66	?	Coexistent
6	Acute	3-52	9-53	1.5	45	2,880	Patient Japanese; Hysterectomy prior to radiation therapy
7	Chronic lymphatic	1947	1956	9	?	?	Low-voltage x-rays, radium needle implant
8	Chronic myeloid	10-50	11-57	7	65	6,200	Plus x-ray
9	Acute	12-53	12-57	4	53	6,400	Plus x-ray
10	Monocytic	1953	1-55	2	43	6,000	Plus x-ray
11	Acute myeloblastic	2-40	1953	13	26	Usual	.....
12	Lymphatic	1-49	1950	1	60	Usual	.....
13	Chronic lymphatic	?	?	0	82	Usual	.....
14	Chronic myeloid	?	?	3.5	?	Usual	.....
15	Chronic lymphatic	?	?	11	?	Usual	.....
16	Chronic lymphatic	?	?	0	?	Usual	.....
17	Chronic lymphatic	?	?	10	?	Usual	.....
18	Chronic lymphatic	5-32	7-47	15	52	7,980	Plus x-ray. Surviving 1958
19	Chronic myeloid	52	54	2	54	7,600	.....
20	Chronic myeloid	?	?	5	?	?	.....
21	Chronic myeloid	53	55	2	?	?	.....
22	Chronic myeloid	?	?	0	?	0	.....

in our series of 16 cases of leukemia, we still include it.

The clinical types of the 16 cases of leukemia (as listed by the collaborators) in this series are as follows:

Acute leukemia	4
Chronic myeloid leukemia	5
Chronic lymphatic leukemia	4
Monocytic leukemia	1
Undetermined type	2
Total	16

It seems to be acceptable to physicians that acute leukemia and chronic myeloid leukemia can be "caused" by radiation but that lymphatic leukemia is unrelated. Evidence for this assumption is based upon the lack of association between chronic lymphatic leukemia and radiation in the "spondylitis" and the "bomb" series of cases. If we deduct the 4 cases of chronic lymphatic leukemia from our series of 16 patients, we have a total of 12 cases of leukemia which might be associated with irradiation. There is now an incidence of only 12 in 71,000 at risk.

As is customary in cancer follow-up studies, these 71,000 cases have been followed for at least five years (and some for as long as fifteen years). During the five years of observation, the percentage of the original patients surviving each year after treatment is approximately as indicated below (1,10).

Years After Treatment	Surviving Patients
1	53,300 (75%)
2	42,600 (60%)
3	35,500 (50%)
4	31,950 (45%)
5	28,400 (40%)
Total person-years at risk	191,750

In our series the incidence of leukemia presumably induced by radiation is 12 in a population of 191,750 person-years at risk, or 62 per million.

Since there is some doubt concerning the validity of the observation that chronic lymphatic leukemia is not associated with radiation, we might include our 4 cases of lymphatic leukemia and

reach the result that there are 16 cases of leukemia in 191,750 person-years at risk.

There is, however, a reasonable possibility that a latent period of one year after irradiation is necessary before induction of leukemia. For this reason we may deduct the number of patients at risk in the first year (53,300). We will include the chronic lymphatic leukemias and even the case of leukemia that occurred in the first year of risk. Thus, our series becomes 16 cases of leukemia in 138,450 person-years at risk or a rate of 115 per million. It then appears reasonable that the incidence of leukemia after radium treatment of cancer of the cervix lies between 62 and 115 per million.

In Great Britain the death rate per million (which is essentially the same as the incidence rate) for leukemia in fifty-five-year-old women is about 58 per million (11); in the United States, in this age group of women the death rate is about 90 per million (12). Population statistics on such small groups are of questionable validity, but the apparent conclusion to be drawn from our study is that the incidence of leukemia after radium treatment for cancer of the cervix is about the same as in the general population of women of the same age group.

The personal opinion of various experts on radiation and cancer of the cervix was considered important in the evaluation of our findings. Carcinoma of the cervix is in a sense the pride of radiotherapy. Our collaborators were interested in discussing these patients, since radium therapy plays a preponderant part in the treatment of this disease throughout the world. Careful follow-up records on these cases are maintained. Relatively few are untraced.

One question posed to our collaborators concerned whether the diagnosis of leukemia could as easily be missed in the general population as in the survivors of cancer of the cervix. Is it likely that in a patient who begins to fail because of leukemia a recurrence or persistence of cancer of the cervix would be mistakenly diagnosed? Responses to this question varied. The consensus was that patients under follow-up care for cancer of the cervix are more likely to have expert medical care and might have more exact diagnoses than would the general population.

It is of great interest that none of the collaborators thought there was an association between radium-treated cancer of the cervix and leukemia and none knew of cases of leukemia in this group without making an analysis of follow-up records.

The further questions that are brought out in a series of this type are not idle speculation, for they indicate whether or not radiation is a proper method of cancer therapy. The data presented in the appendixes of the *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation* (13) indicate poor support for the linear relationship between dose of radiation and leukemogenesis. Abbatt and Lea (14) found a high incidence of rheumatic disease in leukemia patients and concluded that this "precludes the use of such cases [spondylitis] in radiation-induced leukemia dose response investigations."

Wald (15) has summarized the 83 leukemia cases in bomb survivors in Hiroshima from 1945 to 1957. The high incidence of leukemia close to the hypocenter and the decrease far from the hypocenter has a bearing on radiotherapy. The studies of leukemogenesis in radiologists (16, 17, 18), and the studies showing that childhood leukemia may be due principally to other factors more important than radiation (19, 20, 21), also fit into this general problem of radiation leukemogenesis.

The present survey of leukemogenesis in patients treated for carcinoma of the cervix is no better, nor is it any worse, than other studies. It concerns one kind of radiation administered to one kind of patient in one age group.

SUMMARY

Questionnaires concerning the number of leukemia cases developing in survivors of radium-treated cancer of the cervix

were answered by 36 of the collaborators in the *Annual Report on the Results of Treatment in Cancer of the Uterus*. In more than 71,000 patients there appeared 12 cases of leukemia that may have been associated with radiation and an additional 4 cases of chronic lymphatic leukemia. A determination of the person-years at risk shows an incidence of leukemia of from 62 to 115 cases per million. This is essentially the same incidence as in women of similar ages in the United States and England.

It may be concluded, therefore, that radium treatment for cancer of the cervix does not induce an increase in the incidence of leukemia among the survivors.

ACKNOWLEDGMENTS: The authors are grateful to the collaborators listed in Table I and to their associates who so kindly supplied the data and made this presentation possible.

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SUMMARIO IN INTERLINGUA

Radiation e Leucemia in Carcinoma del Cervice

Occurreva, inter 71,582 patientes post radiotherapia pro carcinoma del cervice uterin, 22 casos de leucemia. Post le deduction de 6 casos in que le leucemia esseva presente al tempore del therapia e de 4 casos de chronic leucemia lymphatic (que es generalmente considerate como non relationate con radiation), le cifra final es 12 casos inter 71,000 subjectos in risco.

Le calculation de persona-annos in risco revela un incidentia de 62 a 115 casos per million. Isto es plus o minus identic con le incidentia general in Grande Britannia e le Statos Unite.

Es concludite que le tractamento a radium in cancere del cervice non es associate con un augmento del incidentia de leucemia inter le superviventes.

Scintigraphy and Portography—Their Value in the Diagnosis of Liver Disease[1]

GUNTHER A. DOEHNER, M.D., JOHN C. POWERS, M.D., and FRANCIS F. RUZICKA, JR., M.D.

DEMONSTRATION OF liver disease by radiologic methods has been slow in materializing. One of the more significant developments in recent years has been the introduction of portal venography as a means of liver opacification. This study, developed primarily for visualization of the extrahepatic portal tree, was found to provide fairly satisfactory demonstration not only of the intrahepatic portal branches but also to produce, during passage of contrast medium through sinusoids, a diffuse opacification of liver. The advent of photoscintigraphy has more recently brought still another means of delineating liver disease graphically. It is the purpose of the present essay to present our experience with both scintigraphy and portography in the study of the liver and to compare the two methods to some extent.

TABLE I: CASES EXAMINED

Liver cirrhosis	
Proved clinically	8
Proved by biopsy	7
Total	15
Liver fatty degeneration	
Proved by biopsy	1
Liver carcinoma	
Primary; none metastatic proved by surgery or autopsy	17
Extension from gallbladder carcinoma	1
Total	18
Liver abscess	
Proved by scintigraphy and portohepatography	2
Liver lymphoma	
Proved by biopsy or autopsy	3
Liver focal fibrosis	
Proved by biopsy	1
Normal liver	
Primary neoplasm elsewhere	9
Non eoplastic disease	7
Total	16
Miscellaneous	4
Total	60

MATERIAL AND TECHNICS

The livers of 60 patients were studied by scintigraphy. Table I shows a breakdown of this material by diagnosis. Fifteen of the patients for whom scintigrams were obtained were also examined by splenic portography. These included 7 with cirrhosis, 6 with carcinoma, and 2 with hepatic abscess.

Our experience with splenic portography in the diagnosis of liver disease includes 84 cases (17) with an established diagnosis of liver cirrhosis, separate from this series, and 11 cases (18) of primary and metastatic carcinoma, also distinct from the 6 carcinomas reported.

A. Scintihepatography: A technic projecting the scintigram of the liver directly and simultaneously on the x-ray film was employed. This permits immediate and exact orientation of the scintigraphic findings. This type of projection is achieved by coaxial arrangement of three systems—the collimator, the optical system, and the x-ray beam (Fig. 1).

The patient is so positioned that the radioactivated organ is within the axial area of the system. Collimation is achieved by a central lead cone of 6 and 5 mm. inner diameters and 32 mm. length. The two outer lead cones are 68 mm. in length. The smaller one has inner diameters of 15 and 8 mm., and the larger one diameters of 25 mm. and 13 mm. The three cones are arranged concentrically (Fig. 2). Out of a total crystal surface area of 492 sq. mm., this geometry leaves a central circle and two concentric rings, together measuring 280 sq. mm., available for exposure to radiation. The collimating system has a geometrical focus at 8 cm.

[1] From the Department of Radiology, St. Vincent's Hospital of the City of New York and the New York University College of Medicine. Presented at the Forty-fifth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Nov. 15–20, 1959.

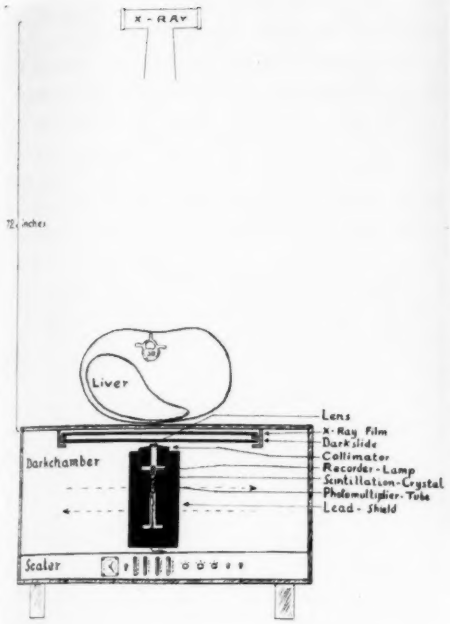

Fig. 1. Schematic cross-section of a photoscintigram with coaxial arrangement of collimator, optical system, and x-ray beam. A gamma ray passing from the radioactivated organ through the collimator to the crystal is converted into a light flash which is projected back in the same direction from which the gamma ray arose and thus to the x-ray film. X-ray exposure is made during the scintigraphic procedure. The light marks of the scintigram outline the radioactivated organ on the x-ray film without appreciable distortion.

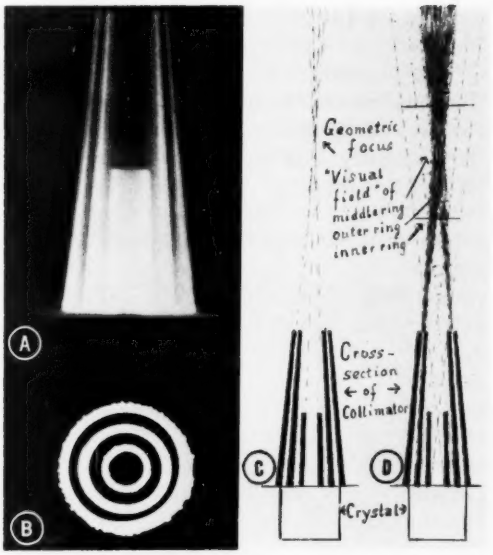

Fig. 2. A. Longitudinal radiograph of the lead collimator. Exposure made with 2,000,000-volt x-ray unit.

B. Cross-section radiograph of lead collimator, at 40 kv. The focus of the x-ray tube was placed in the geometrical focus of the collimator. Note that an inner circle of 28 sq. mm., a middle ring of 106 sq. mm., and an outer ring of 146 sq. mm., of the crystal are exposed to gamma rays.

C. Schematic drawing of the collimator demonstrating the geometrical focus 8 cm. distant from the mouth of the collimator.

D. Schematic drawing demonstrating the radio-optical properties of the collimator. Note the absence of a radio-optical focus, although there is a geometrical focus. Only the outer ring forms a focus of 6 mm. diameter, which is counteracted by the pick-up of the middle ring and the inner circle. The difficulty of obtaining focalized collimation together with loss of crystal surface available for exposure accounts for the failure to demonstrate scintigraphically lesions of less than 2 cm. diameter.

distance from its upper end. The crystal, however, "sees" a cone-shaped space which has a diameter of 20 mm. at 5 cm. from the collimator and 32 mm. at 10 cm. from the collimator.

The superficial planes of the scinti-scanned organ are depicted more sharply but superimposed upon them are the deeper planes, which are slightly blurred scintigraphically with increasing depth. This blurring effect is attenuated by the inverse-square law and absorption in the liver. These technical factors limit the accuracy of projection considerably when organs of greater depth are scintigraphed but they nevertheless permit detection of radioactive defects of more than 2 cm. in diameter.

Mathematical considerations would suggest that activity of superimposed functioning liver tissue might obscure defects of active liver tissue. The ratio of functioning to nonfunctioning tissue must attain a certain threshold value to be scintigraphically noticeable when the two types of tissue are superimposed. From a practical standpoint, by virtue of the effect of the inverse-square law and the absorption in liver tissue, there results a scintigraphic depiction of a representative slice of liver tissue comprising largely the anterior half of the right hepatic lobe and the left hepatic lobe throughout its entire depth. This tomographic-like effect accounts for the fact that the scintigraphic

density of the right hepatic lobe is less than might be expected from its greater depth. It moreover accounts for the fact that metastases in the right hepatic lobe can be scintigraphically demonstrated with only slightly less definition than in the left hepatic lobe.

For sedation Seconal(100 mg.) and Demerol (100 mg.) are given fifteen minutes before the procedure. At the proper time after the injection of the radioactive medium, the patient is placed prone on the scintiscanner, the liver being within the area of the cassette. If, due to ascites or recent abdominal surgical incision, this position cannot be achieved, a slightly right anterior prone position is feasible. Occasionally the supine position must be resorted to. The patient is instructed to avoid any movement and to refrain from deep respiration. The shutter of the cassette is opened, the "scan" is turned on, and radiographic exposure is made. The special cassette uses one intensifying screen on the upper side of the film for intensification of the x-rays. The lower aspect of the film is directly exposed to the light impulses emerging from the center of the collimator. Since only one intensifying screen is employed, the technical factors of radiography are modified. In a patient with an anteroposterior diameter of 20 cm., 100 kv and 100 ma are used, with an exposure time of a quarter of a second.

If I^{131} *rose bengal* is employed, a fatty meal is given three hours after the injection in order to evacuate the radioactive bile from the gallbladder. This is followed by a laxative four to five hours after injection to minimize irradiation of the intestines.

Approximately 7 to 8 microcuries per kilogram of body weight of I^{131} rose bengal is injected intravenously, with routine precautions to avoid radioactive spillage. The scintigram may be preceded by rose bengal liver uptake and excretion tests according to the technic described by Taplin (19). The scintigraphic procedure requires approximately thirty minutes with our equipment at a scanning speed of 15 mm. per second. It should be started at a time when the liver has reached the optimal degree of opacification. This occurs when the uptake curve changes its steep ascent and turns toward its peak—about ten minutes after injection in the presence of normal liver tissue. In the presence of diffuse liver damage, as with liver cirrhosis, the optimal time will be twenty to forty minutes after injection. With suspected metastatic liver disease or liver abscess, the non-involved liver tissue is normal and the scintigram is therefore started at ten minutes and correspondingly later in cirrhosis. In both instances the scintigram will overlap the time of intestinal excretion. This unfavorable factor cannot be avoided with present technics using rose bengal.

If *Aurocolloid* Au^{198} is used, 7 to 8 microcuries per kilogram of body weight is needed for radioactivation of the liver. One hour is sufficient to allow for deposition of the colloid in the reticuloendothelial system of the normal liver tissue. The latter interval is used when dealing with liver neoplasm or abscess. An allowance of two to three hours between injection and scintigraphic procedure is considered advisable if the liver circulation and/or reticuloendothelial uptake are expected to be reduced, as in liver cirrhosis (see below). Although most of the uptake of Au^{198} occurs within the first few minutes of injection, a longer time is needed for obtaining a low blood background.

B. Portography: The technic of splenic portography (percutaneous injection of 70 per cent Urokon into the spleen), as employed in this study, has been described in detail elsewhere (14). It is sufficient to state here that injection of the contrast medium is made into the spleen in ten to fifteen seconds through a No. 19 gauge spinal type needle. Serial films are exposed at two, four, six, eight, twelve, sixteen, twenty-four, and thirty-two seconds following the beginning of injection.

NORMAL PATTERNS

Scintihepatogram: Due to the fluctuation of the atomic disintegrations, the

pattern of the normal scintihepatogram is not perfectly uniform. The irregularity of the disintegration results in a "net-like" pattern which might be compared with the veins of Italian marble (Fig. 3). There are numerous small defects, which, however, "fit" into the net pattern. It may be difficult to differentiate these pseudodefects from multiple small true defects of activity due to metastases. The pseudodefects, however, do not attain a diameter of 2 cm., which represents the smallest true defect identifiable by this technic. On close inspection, it is seen that the pseudodefects do not obliterate all of the "lines" of the photoscintigraphic pattern passing through them.

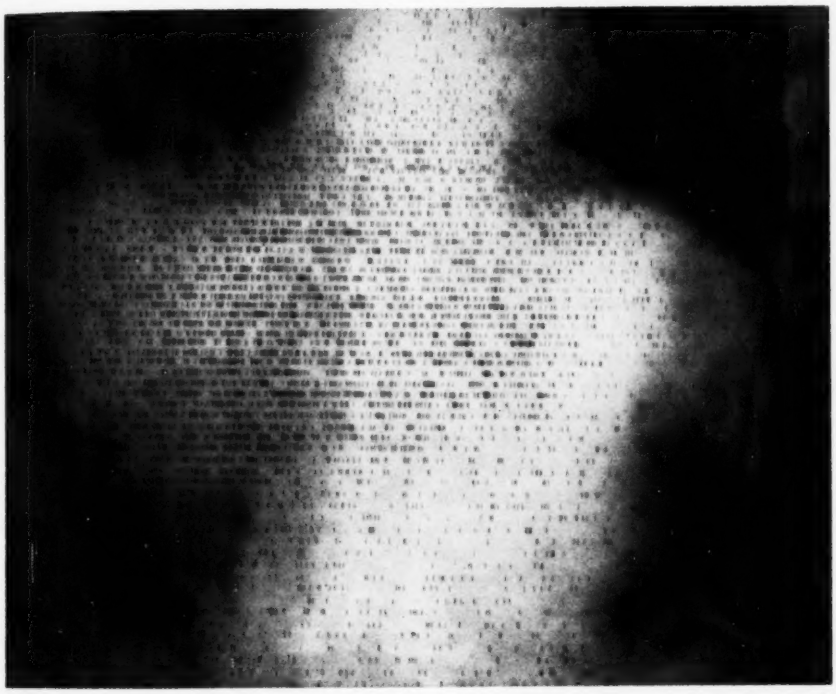

Fig. 3. Scintihepatogram of a 73-year-old white male who was admitted because of signs of bronchiectasis. Liver biopsy was normal. A scintihepatogram done twenty minutes after injection of 400 microcuries of I^{131} rose bengal was considered negative for metastasis. Note the lace-like pattern made by the photoscintigraphic marks. The small defects within the pattern are not defined well enough to be ascribed to metastases. Poor definition of the right margin of the liver pattern here is seen normally (see text).

The net-like pattern is obtained with both rose bengal and radiogold. Although the biochemical mechanism of the liver uptake of the two agents is basically different, scintigraphically the liver acts as a gamma-emitting unit in each instance. The marble pattern becomes less prominent with increasing radioactivity per square centimeter of liver tissue. A minimal scintigraphic intensity per square centimeter of tissue must be achieved technically. Otherwise, erroneous diagnostic conclusions may ensue. The minimum intensity is assessed for practical purposes by inspection of the scintigram. Occasionally an additional dose of the radioactive agent may be required.

The lateral margin of the right hepatic lobe is usually irregularly defined. In contrast to this, the margin of the left hepatic lobe is usually well outlined. With our technic, the activity of the right hepatic lobe is more intense than that of

the left, but not as much so as might be expected from the difference in the anteroposterior diameters of the lobes.

In viewing a photoscintigram, a rather long eye-film distance should be observed. This will result in a more uniform composite impression of the scintigraphic marks. After a general impression is obtained, a close-up evaluation of the lines in local areas may follow. Tangential viewing might be helpful.

Splenoportography: Following splenic injection and the arrival of opaque medium in the liver, the intrahepatic portal vascular tree is demonstrated as a symmetrically branching group of vessels. These taper gradually and present a full complement of large, medium, and small branches. Frequently only the right lobe of the liver is visualized, since layering of the contrast medium, which is of greater specific gravity than blood, produces ready filling of the right main branch (which is more dependent with the patient supine). The left main branch, which occupies a slightly more anterior position, often fails to fill. Following this vasculogram phase (portovasculogram), the contrast medium enters the sinusoidal system of the liver, producing a diffuse homogeneous opacification (portohepatogram) of those areas which showed vessel filling in the vasculogram phase.

CIRRHOSIS OF THE LIVER

Scintigraphic Findings: The scintigraphic findings in cirrhosis follow a rather characteristic pattern. This is modified to some degree by the radiochemical agent used and the time that has elapsed between injection of the agent and the scan. In general, the scintigram, regardless of the radiochemical agent employed, shows a pattern of more or less irregular distribution of radioactivity, depending on the degree of cirrhosis (Fig. 4). The overall radioactivity is low. There are poorly defined defects of diminished activity. Whatever degree of activity and inhomogeneity may appear, the same pattern tends to involve the entire liver equally. The local differences of scintigraphic intensity are small and account for the "uniform inhomogeneity" of the cirrhotic pattern. With fatty degeneration of the liver, a similar pattern is encountered. However, the overall activity is higher with the latter (Fig. 7).

If I^{131} is used and the examination is performed during the period of maximum uptake, the margins of the liver are grossly discernible, though poorly defined (Fig. 4). The poor definition of the liver margin is due to three factors: (*a*) The uptake of I^{131} rose bengal by the hexagonal cells is lowered according to the degree of cell damage caused by the cirrhotic process. This parallels the flattened uptake curve of the liver. (*b*) The blood background remains high because of the deficient clearance by the diseased liver. (*c*) The hepatic excretion, though diminished, is not delayed in time and will begin before the peak of the uptake curve is reached. This results in increased activity in the intestines, which in particular obscures the inferior margin of the liver. All three factors account for the small ratio of the intra- and extrahepatic differential counts and result in decreased definition of the liver.

Scintigraphic differentiation of the cirrhotic pattern from the metastatic pattern may at times be difficult, if not impossible. In these cases the flat rose bengal uptake curve of the liver will suggest the diagnosis. Moreover, even with extensive metastatic involvement and replacement of liver tissue, some area of high normal liver activity may be expected. The only exception is the widespread diffusely infiltrating type of metastatic neoplasm. Islands of high activity indicating normal liver tissue militate strongly against cirrhosis and favor metastasis. The gallbladder usually shows little activity at the time of the examination.

If *radiogold* (Au^{198}) is used (Fig. 5), the inhomogeneity of the liver activity in cirrhosis is similar to that encountered with rose bengal. This finding indicates that in this disease the reticuloendothelial

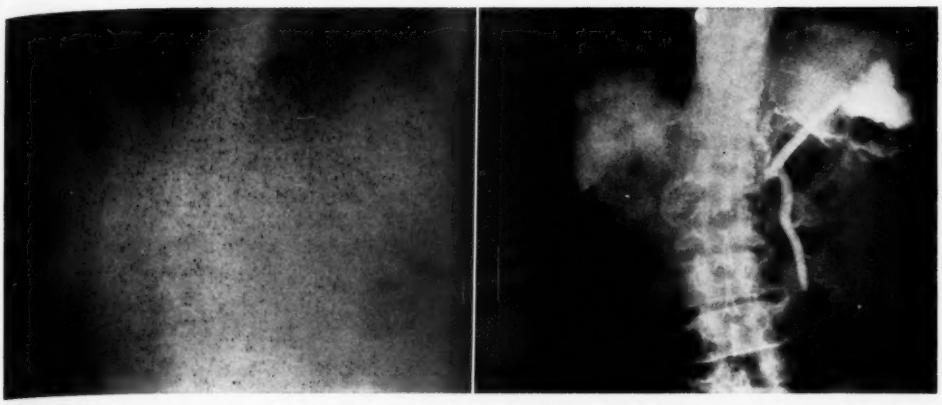

Fig. 4. Cirrhotic pattern in a patient with established clinical diagnosis of cirrhosis and biopsy-proved lung carcinoma. A scintihepatogram made thirty-five minutes after intravenous injection of 500 microcuries of I^{131} rose bengal reveals inhomogeneous and low degree activity of the liver, with poor definition of the margins. The blood background and intestinal background are high.

The portohepatogram demonstrates a mottled pattern and ill-defined margins consistent with cirrhosis. In addition, there are multiple, somewhat poorly defined defects scattered throughout the liver. The latter raised the question of metastasis, although such defects are seen with cirrhosis.

Each examination is diagnostic as far as liver cirrhosis is concerned. Neither examination answers the question, however, of the presence or absence of metastases. The cirrhotic process, which results in a scan of low activity, prevents detection of defects due to metastases which otherwise might be confirmed or excluded by scintigraphy.

system is damaged, as well as the hexagonal cells. The definition of the margin of the liver is usually better with radiogold than with rose bengal, chiefly because the factor of intestinal radioactivity does not exist. Moreover, if the diseased liver is given sufficient time, its reticuloendothelial system will filter out most of the activity from the blood, resulting in a low blood background and even better definition of the margin of the liver.

The left lateral margin of the liver usually adjoins or is superimposed upon the radioactivity of the reticuloendothelial system of the spleen. Normally, the splenic uptake is low and interferes only slightly with the definition of the margin of the left hepatic lobe. In the presence of diffuse liver damage, as for example in cirrhosis, compensatory uptake by the spleen occurs. This may result in an inverted liver/spleen uptake ratio, the uptake of the spleen being equal or higher than that of any segment of the liver. This is readily evident from the scintigram (Fig. 6). This was seen in the minority of the cirrhotic cases. The combination of the cirrhotic liver pattern with a high splenic uptake, in our experience, occurs only with liver cirrhosis and, depending on further confirmation, may become a sign of high diagnostic value.

Even if liver and spleen are superimposed (anatomically or due to regenerative hypertrophy of the left hepatic lobe and splenomegaly), it appears that definite scintigraphic demarcation of the spleen indicates an inverted liver/spleen ratio (Fig. 4).

Splenoportographic Findings: The portovasculogram and portohepatogram in cirrhosis of the liver have been described in detail elsewhere (16, 17). For the sake of clarity, the following changes of the portovasculogram may be noted. A gnarled or tortuous pattern of major vessels is likely to be seen (Fig. 5). Irregularity of caliber, especially of medium-sized and small vessels, frequently develops. A paucity of the small end branches is observed, and at times a very bizarre interlacing pattern of the smaller branches, with complete loss of the normal symmetrical end branching, may be seen. The portohepatogram in cirrhosis most often presents a mottled pattern, which may be fine or coarse. A normal appearing homogeneous hepatogram, however, may

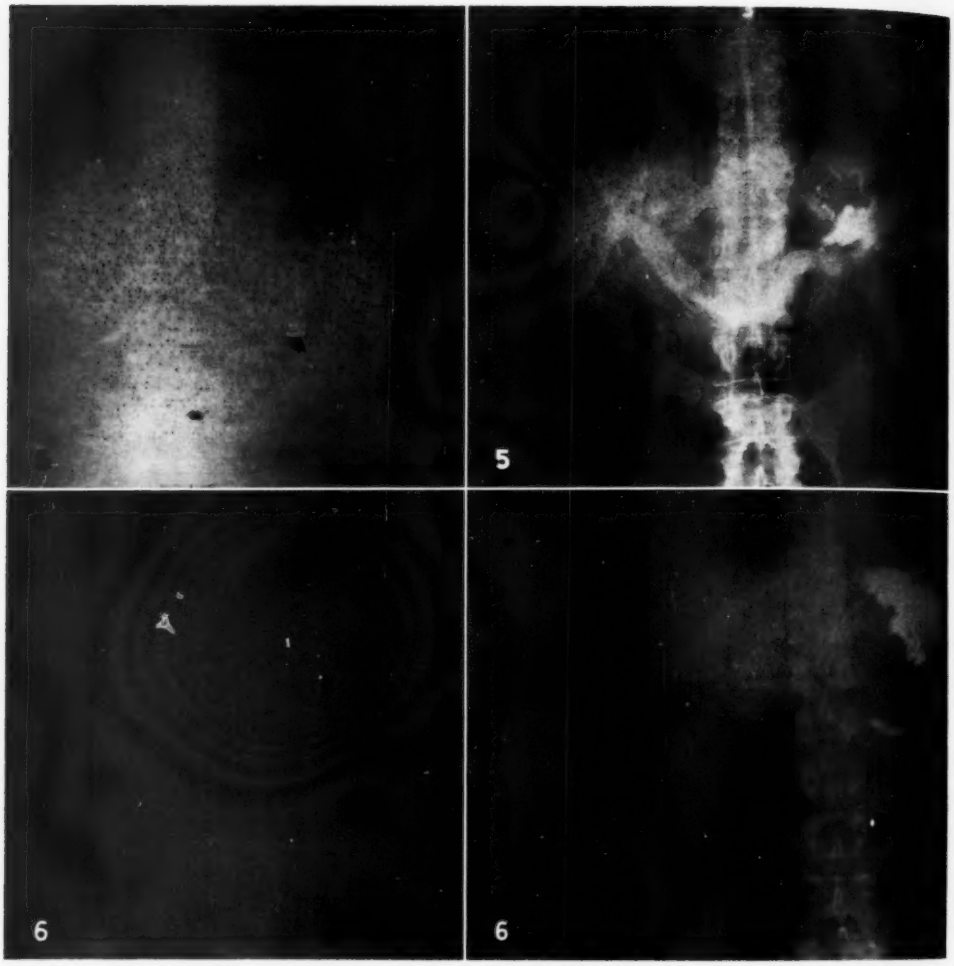

Fig. 5. Scintihepatogram made three hours after injection of 400 microcuries of Aurocolloid 198 in a case of cirrhosis, proved by biopsy, reveals low and inhomogeneous activity, with diminished definition of the margins of the liver. This is characteristic of liver cirrhosis. The activity of the spleen is high. In this case, the spleen is superimposed upon the large left lobe of the liver. The association of a markedly diminished liver uptake with a high splenic uptake is considered typical of liver cirrhosis. Note the high blood background.

The portovasculogram shows a gnarled overall vascular pattern and irregularity of vessel caliber characteristic of cirrhosis. The diagnostic probability is high from either examination.

Fig. 6. Scintihepatogram performed one hour after injection of 500 microcuries of Au 198 in a case clinically diagnosed as cirrhosis, revealing low and inhomogeneous uptake by the liver and poor definition of the margins. Note the increased activity of the splenic area due to the enlarged left hepatic lobe upon which is superimposed the activity of the splenic reticuloendothelial system. Normally, the splenic activity is barely evident from the scintigram. The combination of these findings is typical of liver cirrhosis.

The portohepatogram reveals a mottled pattern typical of liver cirrhosis. Note the large left hepatic lobe which is not infrequently encountered in cirrhosis. Both studies show equally high diagnostic features in this case.

occur with an abnormal vasculogram. Relatively rarely an abnormal hepatogram occurs with a normal vasculogram in cirrhosis. The vasculogram is distinctly positive in 65 per cent of cases (17) and shows some minor changes in an additional 20 per cent. The hepatogram is positive in 55 per cent of cirrhotics.

HEPATIC NEOPLASM

Scintigraphic Findings: When hepatic neoplasm is studied, there is little dif-

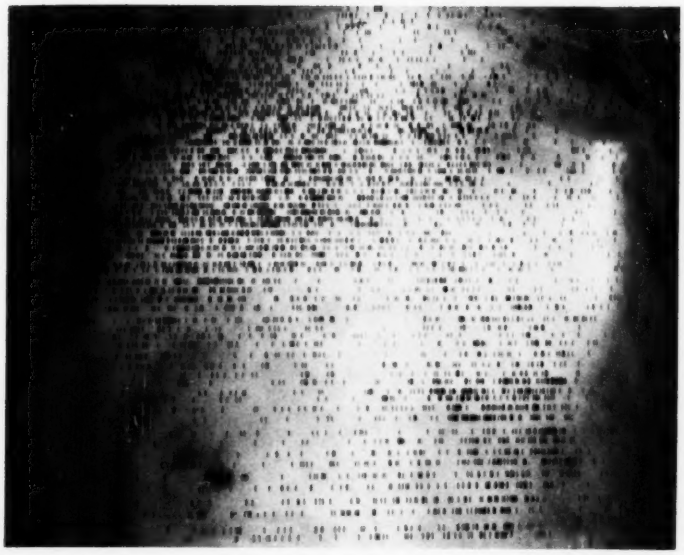

Fig. 7A. Scintihepatogram in case of fatty degeneration of the liver, made twenty minutes after intravenous injection of 450 microcuries of I^{131} rose bengal, reveals inhomogencity of the liver activity and some lack of definition of the liver margin similar to that seen with cirrhosis. However, degree of activity is considerably greater than that expected with cirrhosis. Liver uptake curve was slightly flattened with peak at twenty minutes following injection. Some activity is seen in the jejunum. Note the relatively high blood-intestinal background.

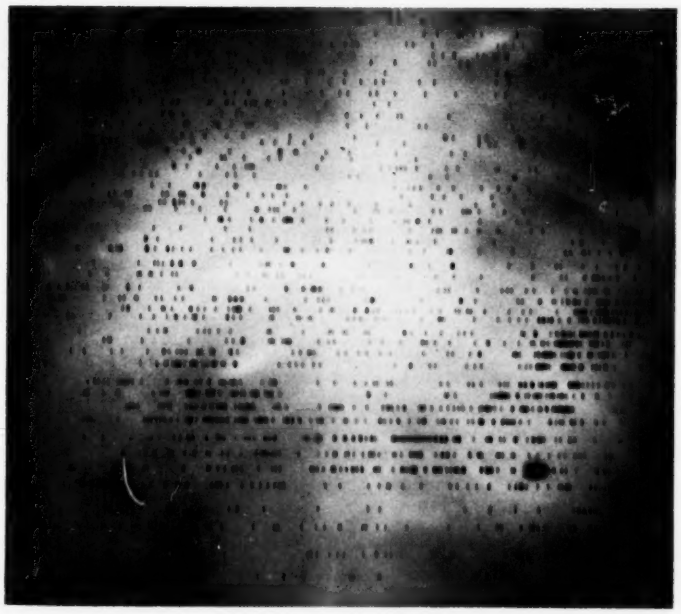

Fig. 7B. Scintihepatogram of same patient as in Fig. 7A, repeated after twenty four hours. The liver has been cleared of radioactivity. Residual activity is now seen in the colon.

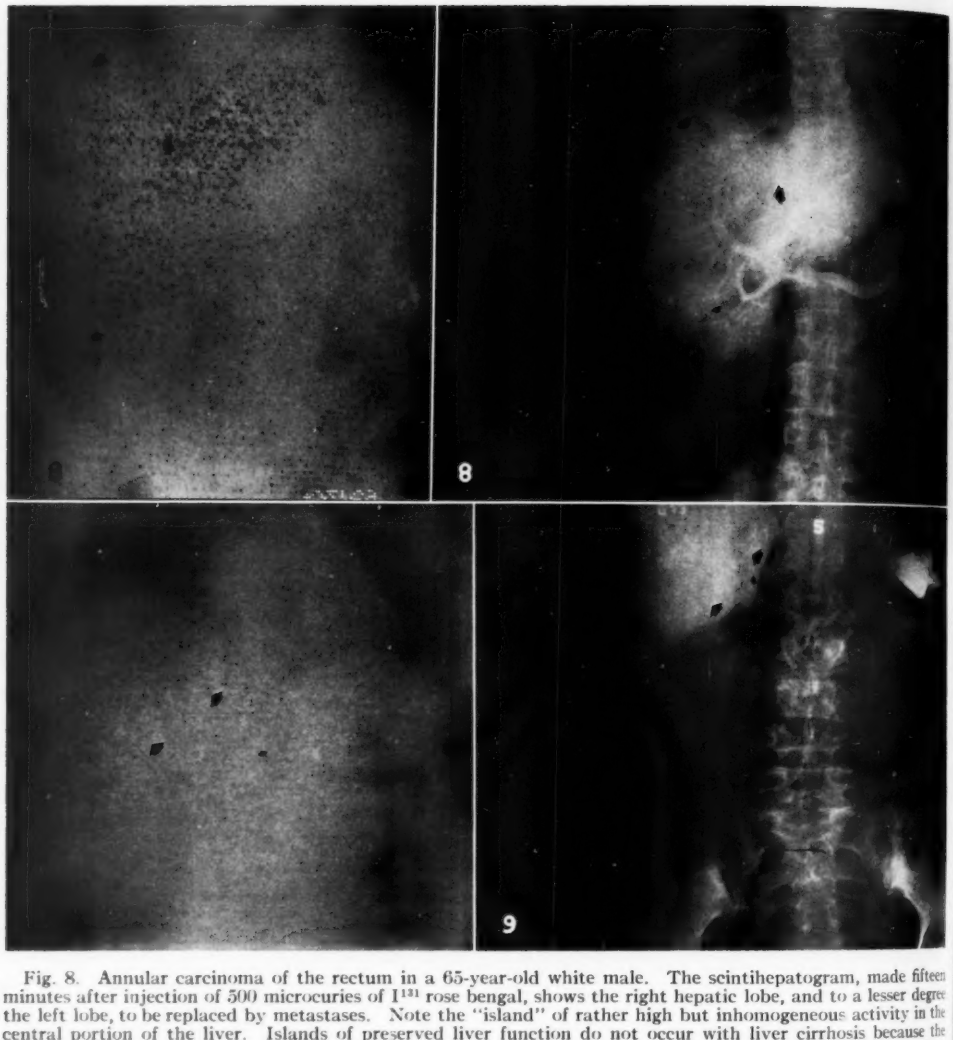

Fig. 8. Annular carcinoma of the rectum in a 65-year-old white male. The scintihepatogram, made fifteen minutes after injection of 500 microcuries of I^{131} rose bengal, shows the right hepatic lobe, and to a lesser degree the left lobe, to be replaced by metastases. Note the "island" of rather high but inhomogeneous activity in the central portion of the liver. Islands of preserved liver function do not occur with liver cirrhosis because the cirrhotic process involves the liver diffusely. This sign, if present, serves to differentiate liver cirrhosis from metastasis.

The portovasculogram and portohepatogram occur concomitantly in this case. The portohepatogram shows defects (large arrows) largely corresponding to the defects in the scintihepatogram. The finer details appear more evident from the portogram, which moreover shows displacement of portal branches (small arrows). A small defect of the left hepatic lobe, however, is evident only in the scintigram (small arrows).

The diagnostic certainty of either examination is high. Together they give a rather complete picture of the extent of metastatic disease in this liver. The high activity in the descending colon is best explained by rapid small intestinal passage caused by watery diarrhea.

Fig. 9. Metastatic pattern in a 67-year-old female with a history of radium therapy to the uterus followed by hysterectomy for a carcinoma of the uterus, now admitted with sciatic pains.

The scintihepatogram, three hours after intravenous injection of 420 microcuries of radiogold, shows a definite defect in the left hepatic lobe (small arrow) and another in the portal area. Another poorly defined defect is seen in the area of the falciform ligament.

The portohepatogram shows multiple well defined defects in the lower and medial portion of the right hepatic lobe. The left hepatic lobe is not opacified.

Each examination affords a high diagnostic accuracy. Together they demonstrate the entire liver. There is good correlation of the scintigraphic and portohepatographic findings, but the smaller defects in the right hepatic lobe are not demonstrated in the scintigram.

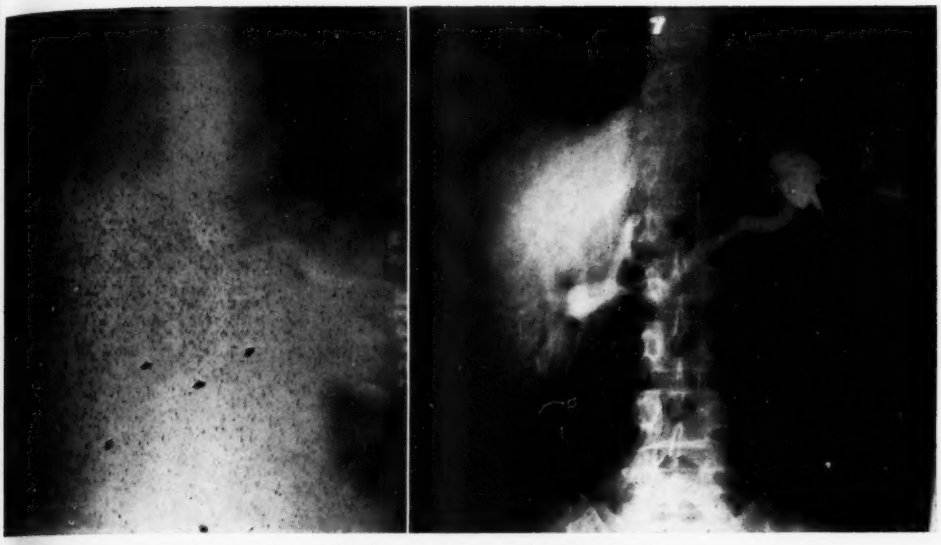

Fig. 10. Recurrent carcinoma of the gallbladder in a 50-year-old white female.
The scintihepatogram performed twenty minutes after injection of 450 microcuries of I^{131} rose bengal revealed a defect at the inferior margin of the liver in the area of the gallbladder. There is inhomogeneous activity of the left hepatic lobe. The portohepatogram shows a similar defect at the inferior margin of the liver. Also present is a radiolucent halo around the larger portal branches at the porta hepatis, which we believe represents tumor infiltrate about the vessels. The left hepatic lobe is not demonstrated in the portogram.

ference, in our experience, whether radioactivation of the liver is obtained with Aurocolloid^{198} or I^{131} rose bengal. Both agents activate the remaining normal liver tissue and demonstrate metastases as defects. Although radiogold is taken up by the reticuloendothelial system and I^{131} rose bengal is accumulated and excreted by the hexagonal liver cells, the liver in either case acts scintigraphically as a gamma-emitting unit. Any replacement of liver tissue by heterogeneous tissue will result in a defect of activity.

In advanced cases of metastatic carcinoma, large confluent defects of irregular outline are seen (Fig. 8). They may occupy any portion of the liver. In most of the cases, areas of well preserved homogeneous normal activity are encountered somewhere in the liver. Smaller metastases (about 2.0 cm. in diameter) appear as roundish, rather well defined defects (Fig. 9). Conglomerates of small metastases below 2 cm. in diameter may create the impression of rather poorly defined defects. Occasionally it is difficult to define metastases at the right lateral margin of the liver, which normally lacks sharp definition with our technic. The smaller metastases were more readily discernible at the upper margin of the left hepatic lobe than elsewhere in the liver. One case of carcinoma of the gallbladder with local extension to liver was studied. This produced a marginal defect similar to that seen with metastatic disease (Fig. 10).

Diffusely infiltrating processes, as for instance certain lymphomas or carcinomas, will closely mimic the pattern of liver cirrhosis. We have encountered no primary carcinoma of the liver in this experience.

Portography: The vasculographic and hepatographic changes in hepatic neoplasm have also been described in detail elsewhere (18). It may be briefly noted that in the vasculogram phase, large nodules in liver often produce a compression-displacement (Fig. 8) effect upon the larger and medium-sized intrahepatic portal branches. Occasionally an intrahepatic portal vessel shows a curvilinear deviation with a pointed ending, due to compression and occlusion—the "thorn sign." This sign

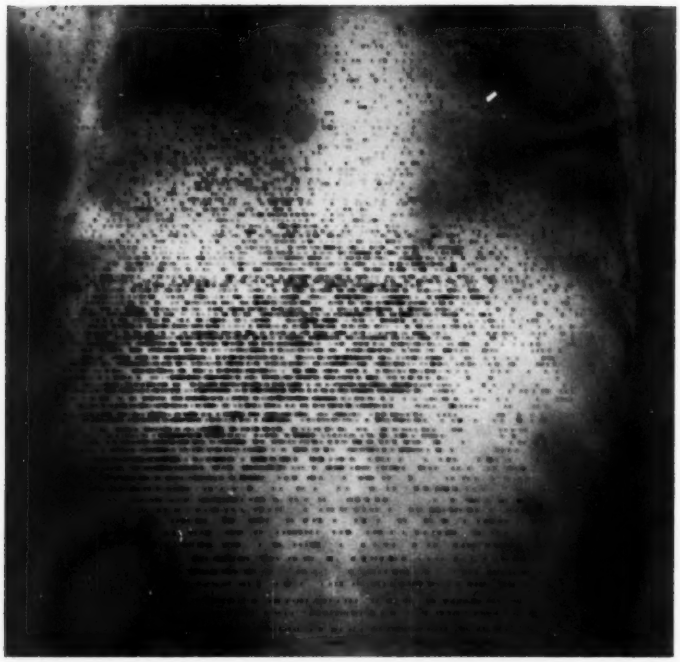

Fig. 11. Amebic liver abscess in a 34-year-old white male from the Virgin Islands who lived in Puerto Rico, Hawaii, and the States. He was admitted with sharp right upper quadrant pain on deep inspiration for three days, "felt sick all over," had had chills and fever and lost 20 lb. in two weeks. Temperature, 103°; white cell count, 26,800, with eosinophilia. Seven stools were negative for parasites.

Scintihepatography with rose bengal revealed a large defect in the upper portion of the right hepatic lobe. Note the tongue-like extension of active liver tissue at the margin of the defect, indicating its intrahepatic location. Following the scan, a stool positive for *Endamoeba histolytica* was examined. Chloroquine therapy cleared all symptoms within twenty days.

Figure 12

(Legend on opposite page.)

was originally observed in July 1954 (G.A.D.) and referred to in later publications. Smaller vessels may be entirely obliterated in certain areas. Smaller lesions, however, may produce very little or no evident effect upon the vessels as seen in the vasculogram when these lesions are scattered, even though they may be numerous. For this reason, the hepatogram phase of sinusoidal opacification is more useful in demonstrating space-occupying deposits in liver (Fig. 9). A technically satisfactory hepatogram will permit identification of individual lesions measuring as little as 1.5 cm. in diameter and groups of multiple but discrete lesions of 1.0 cm. in diameter.

SCINTIGRAPHIC AND PORTOGRAPHIC FINDINGS IN INFLAMMATORY DISEASE

Two liver abscesses have been studied (Table I). These present in the scintigram defects of activity (Figs. 11 and 12) similar to those seen with neoplasm. Diffuse inflammatory disease was not studied.

Portography was used in the same 2 cases. The lesions were poorly defined, perhaps to some extent for technical reasons. However, others (4, 13) have successfully demonstrated liver abscesses. Obliteration and displacement of large and small vessels have been described.

RELATIVE MERITS OF I^{131} ROSE BENGAL AND RADIOGOLD

Scintihepatograms obtained with radiogold 198 and I^{131} rose bengal are approximately equivalent in accuracy in those conditions where there is normal liver tissue between lesions, as in hepatic carcinosis. In liver cirrhosis, Au^{198} appears to be preferable for the following reasons. The definition of the margin of the liver is sharper because of the absence of intestinal radioactivity. Because of the latter, the scan can be delayed until the blood is maximally cleared, which adds to liver border definition. The scintigram can be repeated in case of technical failure without losing quality. Moreover, demonstration of an inverse liver/spleen uptake ratio represents a sign highly suggestive of liver cirrhosis. A disadvantage of radiogold is the higher radiation exposure to the patient (8 rep) to the liver (7). Futhermore, the short half-life of the isotope does not permit any delay of a scheduled examination in a laboratory where precalibrated activity is used. Otherwise, a significant change of the radioactive dose would ensue.

An advantage of rose bengal is that it permits evaluation of the hexagonal cells of the liver if the uptake curve is determined simultaneously. The latter, however, requires the arrangement of two electronic sets and the immediate evaluation of the liver uptake and excretion curves. If this is not done, it is difficult to choose the optimal time for the scintigraphic procedure on the basis of the presumptive clinical diagnosis alone. Thus, the optimal time for this "one-chance" examination may be missed.

When the advantages and disadvantages are weighed and compared, radiogold appears to be slightly preferable to I^{131} rose bengal except in the case of younger patients with the clinical diagnosis of inflammatory lesions. In these cases I^{131} rose bengal, which delivers less total body irradiation, is considered preferable.

RELATIVE MERITS OF SCINTIHEPATOGRAPHY AND PORTOHEPATOGRAPHY

From this experience with both methods used in separate groups of cases and in the same cases, certain conclusions can be

Fig. 12. A 19-year-old Puerto Rican male was admitted with a history of dull but well localized right upper quadrant pain of nine months duration and 20 lb. weight loss. Examination revealed slight hepatomegaly and well localized right upper quadrant tenderness. Stools were negative for ameba and parasites.

A scintihepatogram made fifteen minutes after intravenous injection of 400 microcuries of I^{131} rose bengal revealed a large irregularly outlined defect near the lateral margin of the right hepatic lobe and a smaller defect in the left lobe. The portohepatogram confirmed the defect in the right lobe but showed no abnormality in the left lobe, which was only faintly opacified.

Diagnosis was not further confirmed. The scintigraphic evidence is suggestive of abscess in this particular clinical setting.

reached. In the 7 cases of cirrhosis studied by both methods, the diagnostic accuracy appears to be roughly the same. A certain or highly probable diagnosis was obtained by the scintigraphic method in 4 cases, and by the portographic method in 5 cases. Only 1 case was uncertain by the scanning technic and none was uncertain by portography. In the case in which the diagnosis was doubtful on scanning, it was highly probable by the portographic method. In another case, however, the diagnosis was considered certain on scanning and only probable on portography.

With liver neoplasm, the accuracy of diagnosis also appears to be approximately the same with both methods. The portogram is useful mainly for the right lobe of the liver, whereas the scintigram will demonstrate lesions in the left lobe with much greater effectiveness (Fig. 9). The right lobe can also be depicted by scintigraphy, but there is usually some loss of definition along the right margin of the right lobe. Of the 6 cases of hepatic neoplasm studied by both methods, the diagnosis was certain or highly probable by scan in 2 cases and by portogram in 4 cases. It was probable in 2 cases by scan. A doubtful diagnosis was made twice by each procedure.

TYPE OF INFORMATION

In the splenoportogram there are two phases of liver visualization, the portovasculogram and the portohepatogram. Each of these may give information concerning a particular disease process, and indeed the visualization of the extrahepatic portal system may give considerable supportive evidence of the diagnosis suggested by the vasculogram or hepatogram phases. For example, the demonstration of collateral veins in the extrahepatic portal system would support the diagnosis of cirrhosis suggested by the vasculogram and the hepatogram phases of liver opacification. The presence of a characteristic stenosis of the portal vein due to carcinoma of the gallbladder would support evidence for metastases in the liver suggested by the vasculogram and/or hepatogram phase.

There are certain factors of the scintigram which can also be used as supportive evidence of a disease process. For example, the blood background may be abnormally high in cirrhosis, and this, in conjunction with poor definition of the liver margin and the inhomogeneous activity throughout the entire liver, would support a diagnosis of cirrhosis.

It must be borne in mind that, although the two examinations can be used to demonstrate the same pathological process, they employ different physiological mechanisms. Each method, therefore, may give certain information exclusively which is not provided by the other method. For example, the portogram alone will give an estimate of the degree of actual vascular deformity (Fig. 8) and stasis in the intrahepatic portal veins. The scintigram, on the other hand, will give information on hepatocellular activity not provided by the portogram.

CLINICAL CONSIDERATIONS

In general, the scintihepatogram is more acceptable to both patient and referring physician than the splenic portogram. Although in our experience splenoportography has been a safe procedure when used in accordance with certain basic precautions, there nevertheless exists the chance of complication, chiefly that of splenic hemorrhage. Risk therefore is greater than that expected with the intravenous injection of rose bengal or radiogold. The splenic portogram is at times accompanied by some degree of pain. Although this is usually not severe, the scintigram can be accomplished with practically no pain. The patient occasionally objects to lying prone on the scintigraphic unit for thirty minutes and for some it is quite difficult or even impossible, but in general this is not a problem.

In assessing the relative value of scintihepatography and portography in the diagnosis of liver disease, it can be stated

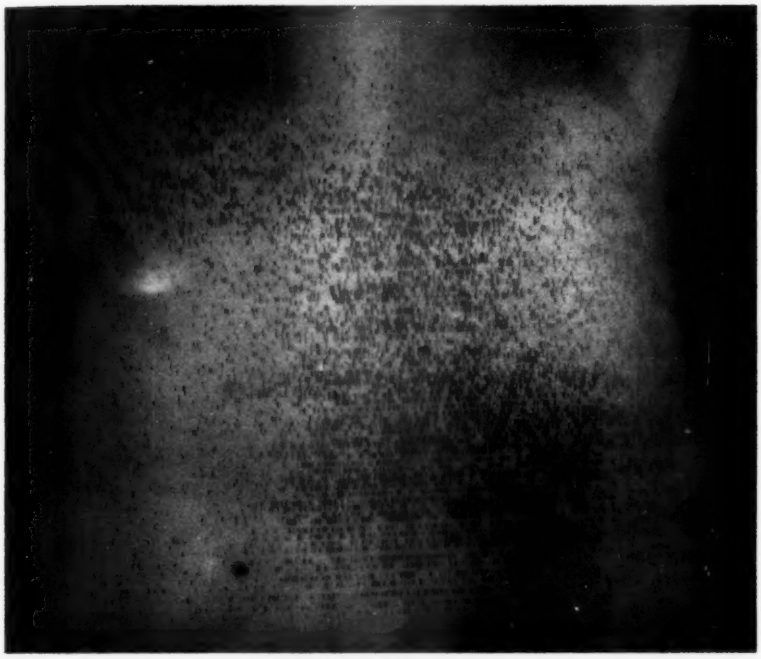

Fig. 13. Congenital anomaly and cirrhosis of the liver. The patient was a 52-year-old white female with almost complete absence of the right hepatic lobe. At a previous hospital admission elsewhere she had been told that she had a cyst in the pancreas and was advised to have an operation, which she refused. She presented a large left epigastric mass. Spleen and liver were not palpable. On x-ray examination, liver and spleen were considered undersized. The left kidney was believed to be enlarged and its contours were distorted.

Scintigraphically the mass proved to be liver tissue of slightly inhomogeneous activity.

At surgery the right lobe of the liver was found to be entirely absent. The gallbladder was lying free on the mesentery. The markedly enlarged left lobe represented the mass. Liver biopsy revealed portal cirrhosis. The activity seen in the scintigram to the right of the midline might possibly represent the activity of the gallbladder, which had fallen over to the right when the patient assumed the prone position. On the other hand, scintigraphically it is impossible to exclude some liver tissue on the right side. The findings were ascribed to an anomaly of the liver, although in view of a proved liver cirrhosis, advanced atrophy of the right hepatic lobe and regenerative hypertrophy of the left lobe must also be considered.

that both methods more or less equally will result in demonstration of all types of more extensive liver pathology excluding diffuse inflammatory conditions.

It has been our experience that, although both studies are apt to portray the disease process present, in an occasional case one method may fail but the other be successful. There are times when both studies, inconclusive separately, may together prove to be quite certain when both show suggestive lesions of the same configuration and in the same place. In general, portographic demonstration of liver disease is more graphic than that obtained with the scintigram (Fig. 8). Possibly in time, with improvement in technic, the scintigram may become equally graphic. Although the portogram often gives more detailed information, the diagnostic certainty from both examinations still may be the same.

CLINICAL APPLICATION

The need for radiologic delineation of pathologic changes within the liver has long been outstanding. The methods of study presented in this paper offer an

approach which is both practical and informative. Neoplasm of the liver can be readily detected. This has occurred in our experience when clinical and laboratory evidence of hepatic metastases has been entirely lacking. The frequent inadequacy of other methods of diagnosis to determine the presence or absence of liver disease is well recognized. The technics of examination described offer a more efficient means of determining operability of the extrahepatic primary carcinoma by virtue of detection of hepatic metastasis. They also, in the case of single liver metastasis, permit a planned approach for segmental resection of the liver itself. It is our practice to employ the scintigram first in such cases, not only because it is more acceptable to patient and referring physician than the portogram but also because it visualizes the left lobe of the liver with regularity. If suggestive but inconclusive data are obtained, the portogram makes a useful corroborative study.

In cirrhosis, the splenic portogram is the method of choice, although the two studies would appear to be equally diagnostic of the cirrhotic change in the liver. The portogram, however, gives desirable information of the portal vascular system answering such questions as the presence or absence of varices and the degree of venous stasis within the liver.

Localized inflammatory processes (abscesses and cysts) are quite readily demonstrated by these examinations. In both instances in our experience, the scintigram gave substance to a clinical diagnosis of liver abscess (Figs. 11 and 12) which otherwise would have been extremely uncertain. Scintihepatography or portography by defining the liver margin may also be used in the differentiation of anomalies and abnormalities of shape of the liver (Fig. 13) from those many lesions that might occur in anatomical relation to the liver such as subdiaphragmatic collections of fluid, infrapulmonary fluid accumulations, eventration of the diaphragm, and subhepatic lesions.

It is our opinion that the scintihepatogram and the portogram offer a means for studying liver which gives information not available in many situations by other clinical and laboratory methods.

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SUMMARIO IN INTERLINGUA

Scintigraphia e Portographia. Lor Valor in le Diagnose de Morbo Hepatic

Le hepates de 60 patientes esseva studiate per scintigraphia post injectiones de rosa bengal a I^{131} o de radioactive auro colloidic. Dece-cinque del serie esseva etiam examinate per splenoportographia. Istos includeva 7 casos de cirrhosis del hepate, 6 casos de carcinoma, e 2 con abscessos hepatic. Pro le studio scintigraphic un technica esseva usate in que le hepate esseva projicite directemente e simultaneemente super le pellicula roentgenographic. Pro le splenoportographia, 70 pro cento de Urokon esseva injicite per via percutanee in le splen, e expositiones serial esseva facite in le curso de un periodo de trenta-duo minutas. Quando le medio opac habeva arrivate in le hepate, un vasculogramma esseva obtenite, sequite per un diffuse opacification homogenee (portohepatogramma) quando le medio entrava in le sinusoides.

In le casos de cirrhosis, le duo technicas pareva esser plus o minus equal in accuratia, e isto valeva etiam pro le casos de neoplasma hepatic. In le casos de lesiones dextero-lobal, le portogramma esseva le plus utile, durante que le scintigramma esseva plus efficace in demonstrar lesiones in le lobo sinistre.

Pro le objectivos del scintigraphia, le auro radioactive pareva esser preferibile al rosa bengal a I^{131}, excepte in le casos de patientes plus juvene con lesiones inflammatori. In tal casos, le secunde substantia applica minus alte doses total de irradiation del corpore.

A generalmente parlar, le scintihepatogramma es plus acceptabile ab le puncto de vista del patiente e etiam ab le puncto de vista del medico qui require le studio. Le risco de complicationes, specialmente de hemorrhagia splenic, es apparentemente plus basse, e le procedura es practicamente indolor.

Es concludite que le scintihepatogramma e le portogramma offere un medio pro le studio del hepate, providente informationes que in multe situationes non es disponibile per altere methodos clinic e laboratorial.

Pulmonary Alveolar Proteinosis—A New Disease?

HENRY P. PLENK, M.S., M.D., SHELLEY A. SWIFT, M.D., WALLACE L. CHAMBERS, M.D., and WESLEY E. PELTZER, M.D.

PULMONARY alveolar proteinosis was described and named, in 1958, by Rosen, Castleman, and Liebow (8), who personally observed 2 cases and examined slides from 25 others sent to them for consultation. Two of our cases were included in this series. One additional case report has been published by Moertel, Woolner, and Bernatz (5), and 2 examples were recently reported by Lull *et al.* (4). Brief mention of 2 cases was also made in a Veterans Administration-United States Army report (7). One other proved case has come to our attention (9). This brings the total number of proved cases, including the 4 examples to be presented in this paper, to 35.

The disease is always confined to the lung and is characterized histologically by the presence of extensive granular eosinophilic material which fills and sometimes distends the normal alveoli. This material stains positively with periodic acid Schiff stain (PAS positive) indicating the presence of mucopolysaccharides. The alveolar walls are usually unaffected, though some thickening and fibrosis of alveolar septa are occasionally seen. Cellular infiltrate is conspicuous by its absence. Peculiar dark-staining, sometimes laminated oval bodies are found in the alveoli.

Rosen *et al.* (8) have postulated that the material in the alveoli is derived from or excreted by the lining septal cells of the alveolar wall and that the oval bodies represent the shed cells themselves. These authors speculate that recently introduced inhalants, such as volatile solvents, aerosols, and insecticides are the most likely cause of the disease.

The clinical manifestations include dyspnea, fatigue, loss of weight, some cough, sometimes fever, and rarely expectoration. On questioning, a history of an earlier acute pneumonitis can often be elicited. Bacteriologic and fungal studies are unrewarding, and no causative organism has been demonstrated.

Adrenocorticoids were used in over one-third of the cases. Only 2 patients, especially 1 reported by Moertel et al. (5), derived definite benefit from Prednisone. Antibiotics were useful in controlling superimposed infections but did not seem to influence the course of the established disease.

Nine of the original 27 patients (8) are known to have died of the disease. One patient died as the result of a cardiovascular accident with persistent pulmonary involvement. Of the new cases (2, 4, 7, 9), including those discussed in this paper, 2 have proved fatal, bringing the mortality to 34 per cent.

MATERIAL

Our material includes 2 cases which were under our observation. One patient is still alive and well after segmental lobectomy; the other died after a rapid downhill course in the hospital. A third case has kindly been supplied by Drs. Elliot C. Lasser and Edward Kent, University of Pittsburgh School of Medicine. A fourth case[2] was seen at the Salt Lake General Hospital and was originally reported (2) primarily for its interesting hematologic finding of thrombocythemia, prior to the description of pulmonary alveolar proteinosis as a disease entity by Rosen *et al.*

[1] From the Departments of Radiology, Pathology, Surgery, and Medicine, St. Mark's Hospital and University of Utah School of Medicine, Salt Lake City, Utah. Presented at the Ninth International Congress of Radiology, Munich, Germany, July 1959, and in preliminary form before the Rocky Mountain Radiological Society, Denver, Colo., August 1958. Accepted for publication in October 1959.

[2] Drs. M. M. Wintrobe and W. R. Christensen, University of Utah School of Medicine, kindly permitted us to review the case and include it in this series.

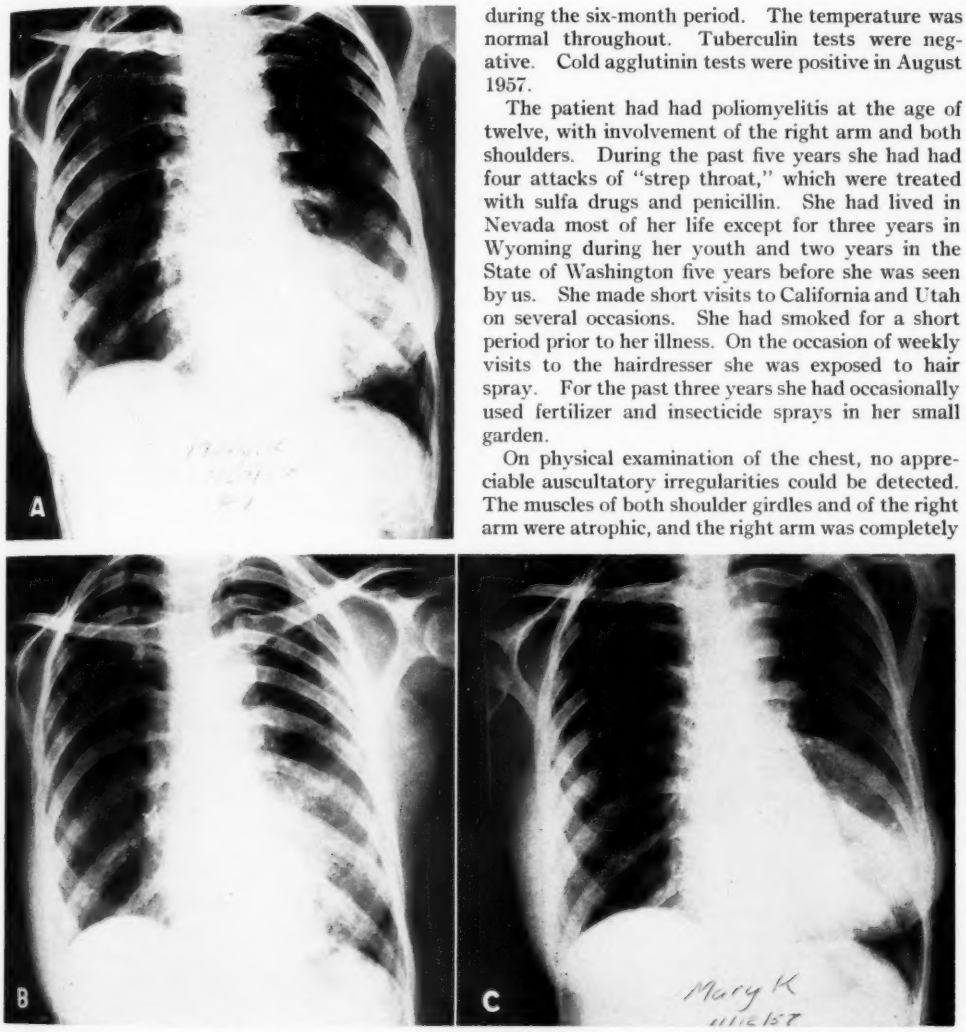

Fig. 1. Case I. A. First examination, May 27, 1957, reveals consolidation of lingula at onset of disease. B. and C. On Nov. 12, 1957, consolidation remains unchanged. Film with left breast elevated (C) shows the disease to be actually in the lung.

CASE REPORTS

CASE I: Mary K., a 42-year-old single school teacher, was first seen at St. Mark's Hospital on Nov. 11, 1957. She had pneumonia in May 1957, for which she was hospitalized in Ely, Nevada. For eight days she received broad-spectrum antibiotics and responded well. She continued, however, to experience some weakness and fatigue, as well as an irregular dry cough and increasing dyspnea on exertion. She gained 12 pounds in six months. Serial films taken at monthly intervals revealed persistent diffuse reticular consolidation of the lingula of the left upper lobe without any appreciable change during the six-month period. The temperature was normal throughout. Tuberculin tests were negative. Cold agglutinin tests were positive in August 1957.

The patient had had poliomyelitis at the age of twelve, with involvement of the right arm and both shoulders. During the past five years she had had four attacks of "strep throat," which were treated with sulfa drugs and penicillin. She had lived in Nevada most of her life except for three years in Wyoming during her youth and two years in the State of Washington five years before she was seen by us. She made short visits to California and Utah on several occasions. She had smoked for a short period prior to her illness. On the occasion of weekly visits to the hairdresser she was exposed to hair spray. For the past three years she had occasionally used fertilizer and insecticide sprays in her small garden.

On physical examination of the chest, no appreciable auscultatory irregularities could be detected. The muscles of both shoulder girdles and of the right arm were atrophic, and the right arm was completely paralyzed as the result of poliomyelitis. Physical examination was otherwise unrevealing. The hematocrit was 44, hemoglobin 14.0 gm., white blood count 7,700 with 70 per cent polymorphonuclear cells. Total proteins were 6.7 gm., the A:G ratio 4.2:2.5, prothrombin time normal, clotting time fourteen minutes (Lee-White). No abnormal urinary changes were found.

X-ray examination (Fig. 1) revealed an area of decreased aeration corresponding to the lingula and the medial basal segment of the left lower lobe. The left breast shadow on the postero-anterior view was superimposed upon the disease process. A film with

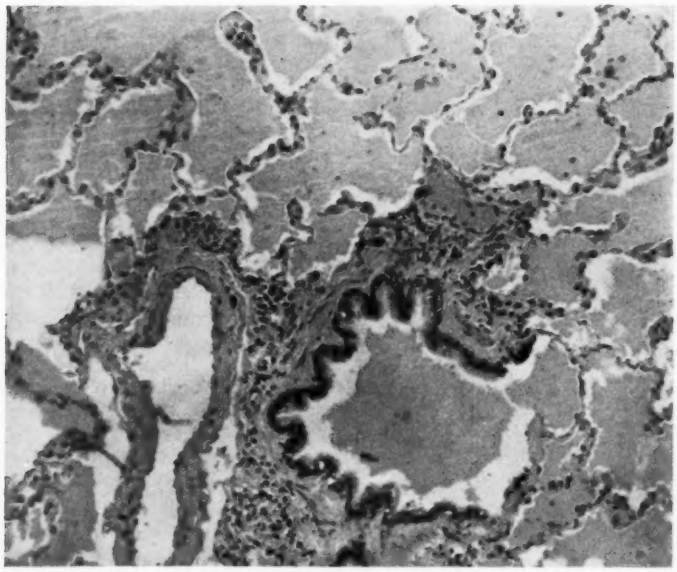

Fig. 2. Case I. Microscopic examination (low power) reveals homogeneous exudate filling alveoli, without thickening of septa or cellular reaction.

the breast elevated convinced us that the disease was actually in the lung. The reticulated, almost finely nodular appearance, with slight decrease in volume of the segment, suggested organized pneumonia as the most likely diagnosis The remaining portions of both lungs were normally aerated. No fluid or pleural thickening could be detected.

On Nov. 13, 1957, a segmental resection of the lingula was performed. A sequestrated segment of the medial basal segment of the left lower lobe was also removed. The postoperative course was uneventful, and the patient was discharged from the hospital on the tenth postoperative day. After experiencing persistent shortness of breath for the first one or two months, she recovered completely, was free of dyspnea and fatigue nine months following surgery, and continues to do well eighteen months later.

The pathologic specimen was described as follows: Resected portions of the lung are of rubbery consistency and nodular to palpation. The sectioned surfaces are homogeneous pink-gray, with scattered foci of yellow. The pleura is smooth and glistening. Both specimens of lung tissue removed showed the same picture.

Microscopic examination (Fig. 2) revealed normal alveolar structure without thickening of the alveolar septa. Most of the alveolar spaces were filled with granular amorphous debris. In a few areas large foam cells were associated with some mononuclear reaction. The complete absence of any specific cellular reaction in the alveoli, the alveolar walls, or the interstitial tissues of the lung was striking. The material stained positively with PAS stain. The immediate tissue diagnosis was pulmonary consolidation of undetermined origin. The picture resembles the description of *Pneumocystis carinii* pneumonitis reported in Europe but only rarely seen in this country. Attempts to culture fungi or other organisms were unsuccessful.

CASE II: Carol B., a 31-year-old colored female, was admitted on Dec. 4, 1957, about three weeks after the first patient. The history revealed progressive weakness, fatigue, nervousness, indigestion, and loss of weight (from 126 to 90 lb.) for two years. The immediate complaints were vague diffuse chest pain and occasional nonproductive cough. The patient was referred for diagnosis and treatment following eighteen days of hospitalization in Rock Springs, Wyoming. She had previously been hospitalized for a week in March 1957 for "pneumonia" and received streptomycin and penicillin. She had also received penicillin for syphilis three or four years earlier. A corneal ulcer was treated in May 1957. Her past history was otherwise noncontributory.

On physical examination the patient appeared severely ill; she was strikingly emaciated, with marked tachycardia and dyspnea. The lungs appeared well aerated on percussion and auscultation. No râles, wheezes, or rhonchi could be detected. The principal laboratory findings were: hematocrit 58; hemoglobin 17.5 gm.; white blood count 9,600 to 14,000 with polymorphonuclears 69, lymphocytes 25, monocytes 6; sedimentation rate 6 mm. in one hour; serologic test for syphilis negative; no urinary abnormalities; total protein 7.8 gm.; albumin 4.3 gm.; globulin 3.5 gm.; A:G ratio 1:2. Paper electrophoresis revealed a normal pattern. The skin tests for histoplasmin,

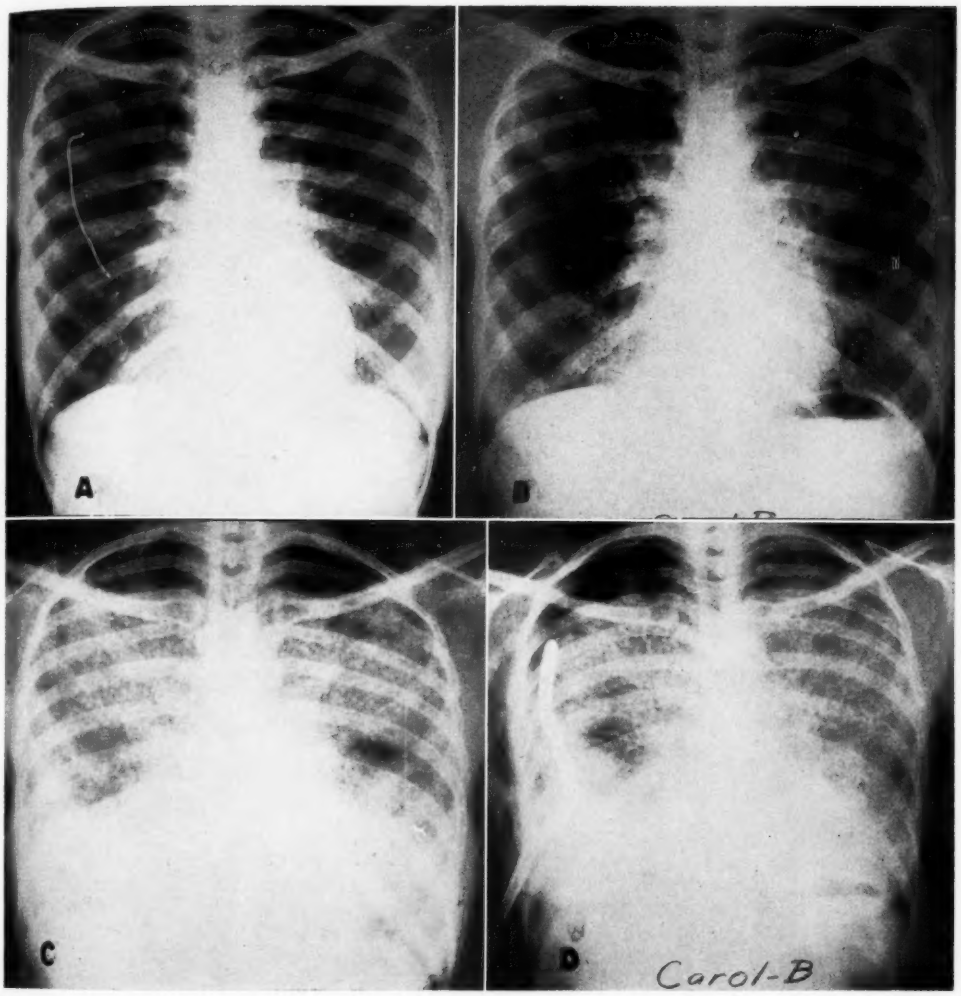

Fig. 3. Case II. A. First examination, Sept. 13, 1956, reveals fine nodularity and slight exaggeration of pulmonary markings.
B. Second examination, March 13, 1957, shows feathery densities extending almost symmetrically from both hili into the periphery.
C. Third examination, Nov. 15, 1957, shows progressive diffuse consolidation with confluent patches.
D. Appearance of chest post-thoracotomy, two days prior to death.

coccidioidin, blastomycin, and tuberculin first and second strength were negative. Agglutination tests were negative for brucellosis but positive for tularemia in 1:200 dilution.

A chest film taken in September 1956 (Fig. 3,A), fourteen months prior to admission, revealed a slight but diffuse fine nodularity of both lungs. Progressive, feathery, slightly nodular densities distributed symmetrically throughout both lungs with increase in the hilar shadows were apparent on films of March 13 and Nov. 15, 1957. No fluid was present in either pleural cavity. The x-ray appearance was most suggestive of sarcoid but resembled the recent case of Mary K. (Fig. 3, B and C).

On Dec. 9, 1957, a lung biopsy was performed. The patient tolerated the procedure fairly well, but severe dyspnea and tachycardia persisted and she expired suddenly on the fourth postoperative day. The lungs appeared to contain a diffuse "suppurative" process.

On postmortem examination residues of pelvic inflammatory disease and passive congestion of the liver, spleen, and kidneys were found. Otherwise, abnormal findings were confined to the chest. The

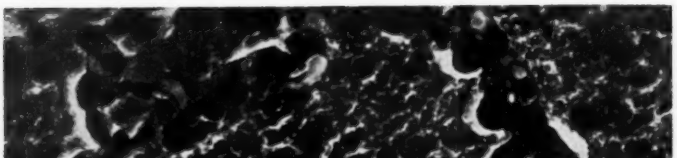

Fig. 4. Case II. Microscopic examination shows alveolus filled with granular PAS-positive material with several dark-staining oval bodies. Proliferation of septal cells lining alveolar wall. High power.

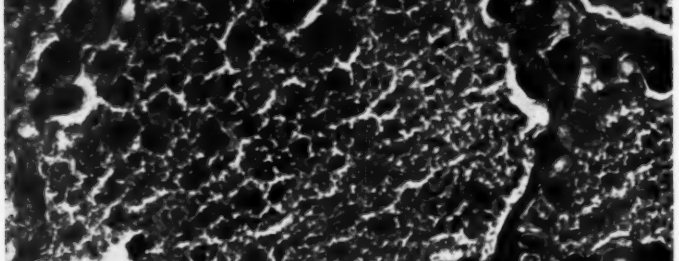

Fig. 5. Case III. Microscopic examination (high power) reveals dark-staining oval bodies in alveolus filled with granular material.

wall of the moderately dilated right ventricle was about twice the normal thickness; the left ventricle was normal. The left lung weighed 870 grams, the right 1,000 grams. Both lungs were completely consolidated and retained their shape after removal. They were of a firm rubbery consistency and sank when placed in water. Soft mucoid material could be scraped from the light cream-colored sectioned surfaces. No abscesses were present. Bronchial lumina were patent. Microscopic examination (Fig. 4) revealed filling of almost all alveoli by PAS-positive granular material with many dark-staining bod-

ies and only localized thickening of occasional alveolar septa.

Final Diagnosis: Pulmonary alveolar proteinosis; cor pulmonale.

CASE III (Courtesy of Drs. Lasser and Kent, Pittsburgh, Penna.): E. T., a 41-year-old white male, was admitted to Presbyterian Hospital on Aug. 7, 1958, with intermittent chills, fever, and hemoptysis of four years duration. He gave a history of "pneumonia" with hemoptysis, which was treated by his local physician at home four years previously. During the past four years he had experienced intermittent episodes of chills, fever, and hemoptysis, averaging three times a year and responding to Achromycin. During the intervening periods he had a persistent cough, productive of clear yellow sputum. Three years previously, a "normal" chest film was obtained (elsewhere) and a bronchogram was diagnosed as "bronchiectasis." An "abnormal" chest film was reported in May 1957. There had been a 10-pound weight loss. The patient was a crane operator. He had worked around varnish tanks and more recently with paints. X-ray examination on admission (Fig. 6) revealed bilateral patchy areas of consolidation throughout the right lung and the lower half of the left lung.

Physical examination was essentially negative. Occasional temperature elevation of 1° was noted during hospitalization. The blood count was normal, with total protein 7.3 gm., albumin 3.6 gm., and globulin 3.7 gm. Serum paper electrophoresis revealed a marked increase in alpha 2 globulin. Exploratory thoracotomy with wedge resection resulted in the diagnosis of pulmonary alveolar proteinosis (Fig. 5).

CASE IV (Courtesy of Drs. M. M. Wintrobe and W. R. Christensen): A 19-year-old white female was first seen in October 1954, with a history of dyspnea of three months duration and weight loss of 14 lb. Following a tonsillectomy in August 1952, a massive hemorrhage required a transfusion of 4 units of blood. An increased buffy coat was noted in the hematocrit tube. Excessive menstrual bleeding and anemia occurred during the next year. A chest film taken in November 1953 was normal. In August 1954, the patient began to notice progressive dyspnea, intermittent nonproductive cough, and weight loss. On admission, Oct. 15, 1954, physical examination revealed slight cyanosis of lips and nail beds. Findings were otherwise irrelevant. There was no fever. Extensive bilateral diffuse, finely nodular infiltration with some coalescence in the left second anterior interspace was observed on x-ray examination (Fig. 7, A). On Oct. 21, the left upper lobe was found to be consolidated (Fig. 7, B). The patient's condition improved following treatment with tetracycline, but on the twelfth hospital day a spontaneous pneumothorax developed (Fig. 7, C). She was discharged on the forty-ninth hospital day. Subsequent films disclosed progressive

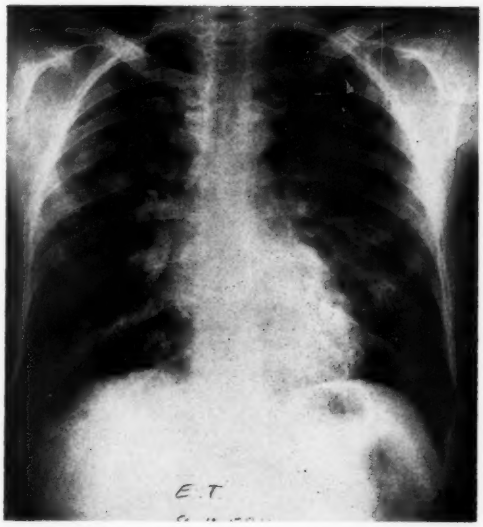

Fig. 6. Case III. Admission roentgenogram showing bilateral patchy areas of consolidation.

coalescence of feathery and nodular densities of the right lung but some resolution on the left (Fig. 7, D).

Laboratory examination revealed striking thrombocytosis (3 million + platelets per cubic millimeter), a moderate leukocytosis (20,000), and an increased erythrocyte count (6.33 million). Bacteriological studies were reported as follows: Predominant organisms in cultures during hospital stay: nonhemolytic, alpha hemolytic, and beta hemolytic *Streptococcus*, nonhemolytic coagulase-positive *Staphylococcus aureus*, *Candida albicans*. Other hematologic and pulmonary function studies and autopsy findings have been previously reported in detail (2).

Postmortem examination revealed findings very similar to those in our second case. The most striking were a diffuse intra-alveolar noncellular coagulum in the lungs and a marked increase in megakaryocytes in the bone marrow. More fibrosis and cellular infiltration of alveolar septa were seen in this case than in any other. It should be classified as another example of pulmonary alveolar proteinosis.

A complement-fixation test with antigen prepared from a fatal case of *Pneumocystis* pneumonia was described by Vivell *et al.* (11) as very specific for *Pneumocystis* disease. The serum of our surviving patient (Case I) reacted positively to this antigen on three occasions. We therefore thought it worthwhile to test the sera of all known surviving patients with pulmonary alveolar proteinosis against this antigen.

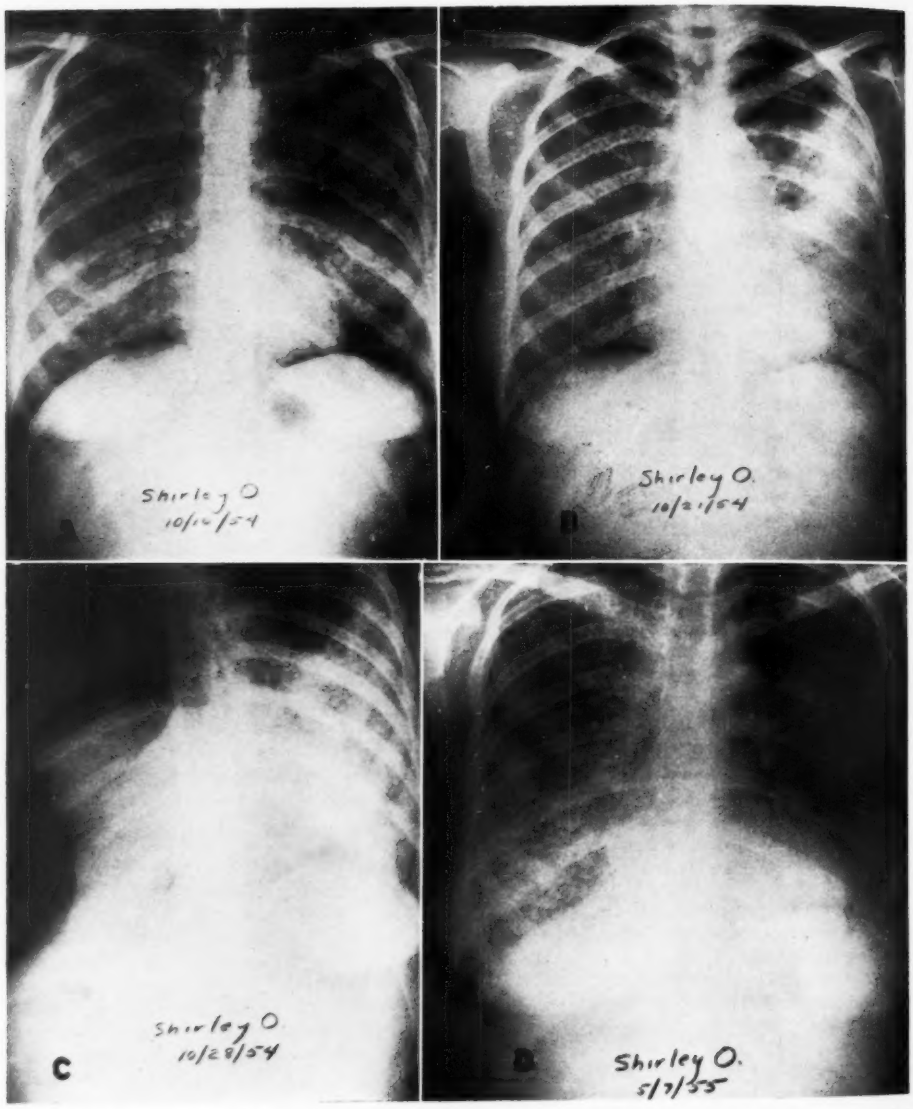

Fig. 7. Case IV. A. Chest film, Oct. 16, 1954, one day after admission, revealing feathery, somewhat confluent areas of consolidation, especially in both lower lobes.
B. Film five days later, showing an additional area of homogeneous consolidation in the left upper lobe.
C. Spontaneous right pneumothorax resulted in massive collapse of the right lung, Oct. 28, 1954.
D. Considerable resolution of the consolidation of the left lung has taken place, May 7, 1955, but increased confluence of patches of density is seen in the right lower lobe.

With the co-operation of many doctors throughout the United States, we were able to obtain sera from 8 additional survivors in whom the diagnosis had been proved. The results of the complement-fixation tests were as follows:

Positive
Mary K. (Our Case I)
Roosevelt R. (4)
Orville G. (8. Case 11)
Alice W. (8. Case 19)

Negative
Lucille S. (4)

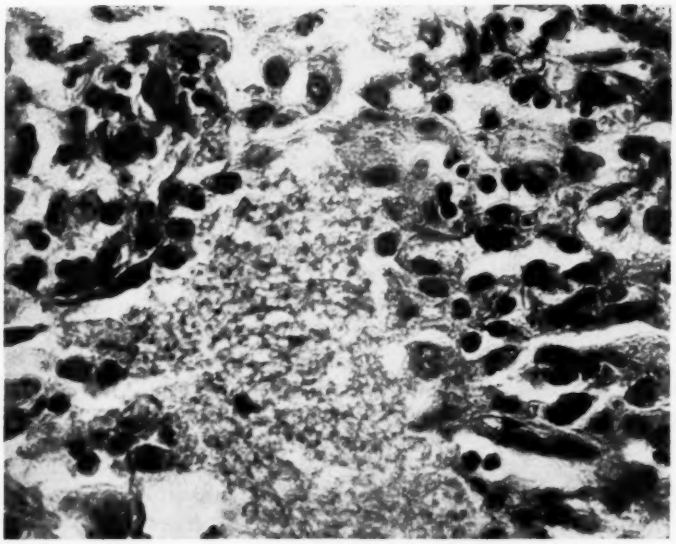

Fig. 8. *Pneumocystis* pneumonia (courtesy of Dr. Ariztia, Santiago de Chile). The PAS-positive material in the alveoli is definitely "foamy." More cellular reaction and thickening of the alveolar septa are apparent. High power.

Otis W. (9)
Alice P. (8. Case 6)
David M. (8. Case 16)
Hubert W. (8. Case 17)

No positive reactions were obtained in normal controls or in patients with pulmonary disease other than pulmonary alveolar proteinosis.

DISCUSSION

A certain similarity between the disease entities of pulmonary alveolar proteinosis and interstitial plasma-cell pneumonia (*Pneumocystis carinii* pneumonia) was pointed out by Rosen *et al.* (8). In fact, 2 of their 27 collected cases were previously reported as *Pneumocystis* pneumonia. Our initial diagnosis of our first case also was *Pneumocystis* pneumonia. When the slides were sent to various authors on the subject in this country and abroad for confirmation of the diagnosis, the replies were far from unanimous. Those most experienced with *Pneumocystis* pneumonia, however, were quite convinced that our case represented a different disease entity. Dr. Averill Liebow (3) of Yale University pointed out that he had collected 16 cases similar to ours by November 1957. This number increased to 27 in the next six months.

The similarity of the two diseases is found in the clinical manifestations, x-ray findings, and in some histologic features. Both pulmonary alveolar proteinosis and *Pneumocystis* pneumonia often start insidiously. The presenting symptoms in each are frequently malaise, loss of weight, anorexia, low-grade fever, but relatively little cough and expectoration. The lack of physical findings in the presence of widespread pulmonary disease demonstrable roentgenologically is a striking feature of both conditions.

Roentgen findings in both pulmonary alveolar proteinosis and *Pneumocystis* pneumonia may be protean and resemble pulmonary edema, Boeck's sarcoid, diffuse bronchopneumonia, or some of the pneumoconioses. Changes are usually bilateral and often diffuse. In our Case I the disease process was apparently confined to parts of one lung, making successful segmental resection possible. Interstitial emphysema and pneumothorax have been observed in both diseases. Complete resolution has occurred in a number of cases of

Pneumocystis pneumonia (*e.g.*, Sternberg and Rosenthal, 10), and at least one well documented case (1) of complete resolution of pulmonary alveolar proteinosis demonstrated by x-ray has come to our attention.

Pathologically, the lungs in both diseases are grossly firm, rubbery, and heavier than water. Sectioned surfaces are pinkish-gray, fleshy, and nodular. The trachea and bronchi are usually not involved. Lymph nodes are rarely affected. The pathologic findings in both conditions are confined to the lungs.

Microscopically the similarity consists in the presence of masses of PAS-positive material filling the alveoli. However, while this material is granular to homogeneous in pulmonary alveolar proteinosis, it is definitely foamy or cystic in *Pneumocystis* pneumonia (Fig. 8), the cystic spaces supposedly representing the causative organism. *Pneumocystis carinii* sometimes displays definite spore formation in multiples of two. No cysts or spores have ever been demonstrated in cases of pulmonary alveolar proteinosis.

The results of the complement-fixation test are most interesting. Though the occurrence of 4 positive reactions in 9 cases is far from conclusive, it may be of real significance. Vivell (11) found that even in Central Europe, where *Pneumocystis* pneumonia is endemic, few adults react positively to the antigen. A high percentage of nurses in close contact with affected infants had positive complement-fixation tests but the titers disappeared rapidly when contact with sick children was discontinued. It is entirely possible that all patients with pulmonary alveolar proteinosis at one stage of their disease may react positively but that the titer of antibodies decreases in the course of time. It seems quite unlikely that a large number of the United States population would react positively to *Pneumocystis* antigen, as the disease in the United States has been found only very sporadically in the past three years.

Indeed, we would be on rather tenuous ground to propose that pulmonary alveolar proteinosis is caused by *Pneumocystis carinii*. If this were the case, more cases of pulmonary alveolar proteinosis should be found in Europe, where the disease is endemic, rather than predominantly in the United States. Other factors could cause a variant. All cases of pulmonary alveolar proteinosis have occurred since 1953. All of our cases and most, if not all, other reported cases have been treated by antibiotics, often broad-spectrum antibiotics, at the onset of the disease or for prior illnesses. Antibiotics might change the resistance of the body to an otherwise nonpathogenic organism or modify the bacterial flora to allow some such organism to grow. This appeals to us much more than the hypothesis of inhalation of new chemicals as the cause for the disease. Even if *Pneumocystis carinii* is not likely to be the causative agent, we cannot dismiss the possibility of another antigenically related organism as the cause of pulmonary alveolar proteinosis.

A renewed argument regarding the etiology of *Pneumocystis* pneumonia is reappearing in the literature. The question of virus origin of the disease is being raised. While Moser (6) suggested that a large virus belonging to the group which includes psittacosis is responsible for *Pneumocystis* pneumonia, Vivell and Lips (12) conclude that the causative factor of plasma-cell pneumonia in infants is not a member of the adenoviruses.

In pulmonary alveolar proteinosis, Rosen *et al.* (8) are convinced that the alveolar material is derived from the living alveolar cells. It is difficult to believe that the occasional septal cell should be capable of producing such massive amounts of "proteinaceous" material. Could it not be that its presence in these cells is evidence of phagocytosis rather than of production?

The immunologic approach holds promise of shedding further light on the etiology of a still mysterious disease.

SUMMARY AND CONCLUSIONS

1. Four cases of pulmonary alveolar proteinosis are reported.

2. The disease is characterized by insidious onset, with fatigue, loss of weight, progressive dyspnea, cough, and slight fever as the most common manifestations.

3. X-ray findings vary from fine nodular to feathery consolidation localized to isolated lung segments to widespread bilateral, often symmetrical, confluent densities involving an entire lung.

4. A total of 35 cases have been identified, with a mortality rate of 34 per cent.

5. Four of 9 patients reacted positively to a complement-fixation test with an antigen from a fatal case of *Pneumocystis* pneumonia.

6. It is speculated that the cause of the disease may be an organism, possibly antigenically related to *Pneumocystis carinii*, rather than inhalation of new volatile agents. The possibility of some virus being the cause of both pulmonary alveolar proteinosis and *Pneumocystis* pneumonia has not been ruled out definitely.

7. The possible role of antibiotics in the etiology of the disease is discussed.

ACKNOWLEDGMENT: We are greatly indebted to Dozent Dr. Oskar Vivell, Freiburg/Breisgau, Germany, for performing many of the complement-fixation tests; to Dr. J. Schmidt, Leipzig, East Germany, for supplying us with some antigen; to the numerous pathologists in the United States and abroad who kindly reviewed our slides; and to Drs. E. J. Eichwald and R. Y. Card for review of the manuscript. Special thanks are due to the following physicians who were kind enough to obtain sera for complement-fixation tests: George F. Lull, Jr., Denver, Colo.; Thomas F. Snider, Dearborn, Mich.; Herman S. Dick and M. Kutzer, Syracuse, N. Y.; Victor Gehring, Leavenworth, Wash.; Ferdinand Helwig and Maxwell G. Barry, Kansas City, Mo.; Robert G. Dunn and David Merren, Albany, Ga.; Walter H. Sheldon, Atlanta, Ga.; David Singman, Richmond, Calif.

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SUMMARIO IN INTERLINGUA

Proteinosis Pulmono-Alveolar—Un Nove Morbo?

Es reportate quatro casos de proteinosis pulmono-alveolar. Le morbo es characteristate per un declaration insidiose, con fatiga, perdita de peso, evidentia progressive de dyspnea, tusse, e leve grados de febre como le manifestationes le plus commun. Le constatationes roentgenoscopic varia inter finmente nodular o plumose consolidationes situate in segmentos isolate del pulmon e extense confluente densitates del pulmon total que es bilateral e frequentemente symmetric.

Un total de 35 casos ha essite identificate, con un mortalitate de 34 pro cento. Quatro ex 9 patientes reageva positivemente al test de fixation de complemento con un antigeno obtenite ab un

caso mortal de plneumonia per *Pneumocystis*.

Es speculate que le causa del morbo es un organismo, possibilemente relationate antigenicamente a *Pneumocystis carinii*, plus tosto que le inhalation de nove agentes volatile. Le possibilitate que un virus es le causa de proteinosis pulmono-alveolar e etiam de pneumonia a *Pneumocystis* non es definitemente excludite.

Le rolo possibile de antibioticos in le etiologia del morbo es discutite.

Unilateral Hypertrophy of the Mandibular Condyle

Report of a Case and Review of the Literature[1]

IRVING WEISSMAN, M.D.[2], and EDMUND M. COLLINS, M.D., D.D.S.[3]

DISTURBANCES of the temporomandibular joint are not uncommon, but positive x-ray findings are frequently absent in patients with disabling symptoms related to this joint. It is always gratifying to the radiologist to be able to present to his consultant, and in turn to the patient, radiographic evidence to explain the cause of a disability. Condylar hypertrophy is a rare entity of unknown etiology, causing facial deformity and malocclusion. It may be unilateral or bilateral. The roentgenologic features are characteristic and certainly account for the symptoms. The condition is progressive, becoming manifest in early adulthood. Zanca and Murphy (10) describe it as a benign disease. In unilateral cases the enlargement of the head of the condyle, associated with elongation of the ascending ramus of the mandible, causes a lowering of the angle of the jaw and a shift of the symphysis menti to the unaffected side, giving, as in the case presented here, the impression of a tumor growing on the normal side. It is this combination of progressive facial deformity, plus the fear of a growing tumor, that brings the patient to a doctor. Pain is not an outstanding symptom and may be absent until the disease has progressed to the stage of well marked deformity.

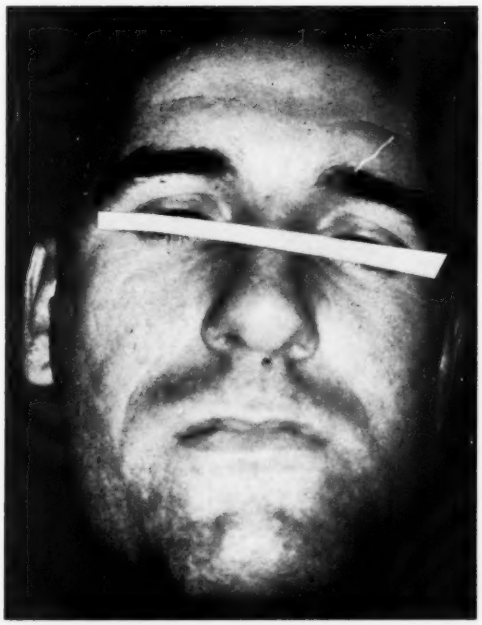

Fig. 1. Frontal view showing asymmetry of lower jaw.

Fig. 2. Frontal occlusal view showing the open bite, primarily on the right side.

As already indicated, the etiology is obscure. Van Zile (8) believes the disorder to be comparable in many respects to the single cartilage-covered exostoses of the long bones. Both occur at sites where precartilaginous tissue persists through a greater part of life. The principal difference appears to be that, in the case of the jaw, the excess bone is often remolded to serve a functional purpose. The entity, therefore, has been variously reported as osteoma or exostosis of the condyle. Some authors (3–6, 9) state that unilateral hypertrophy of the con-

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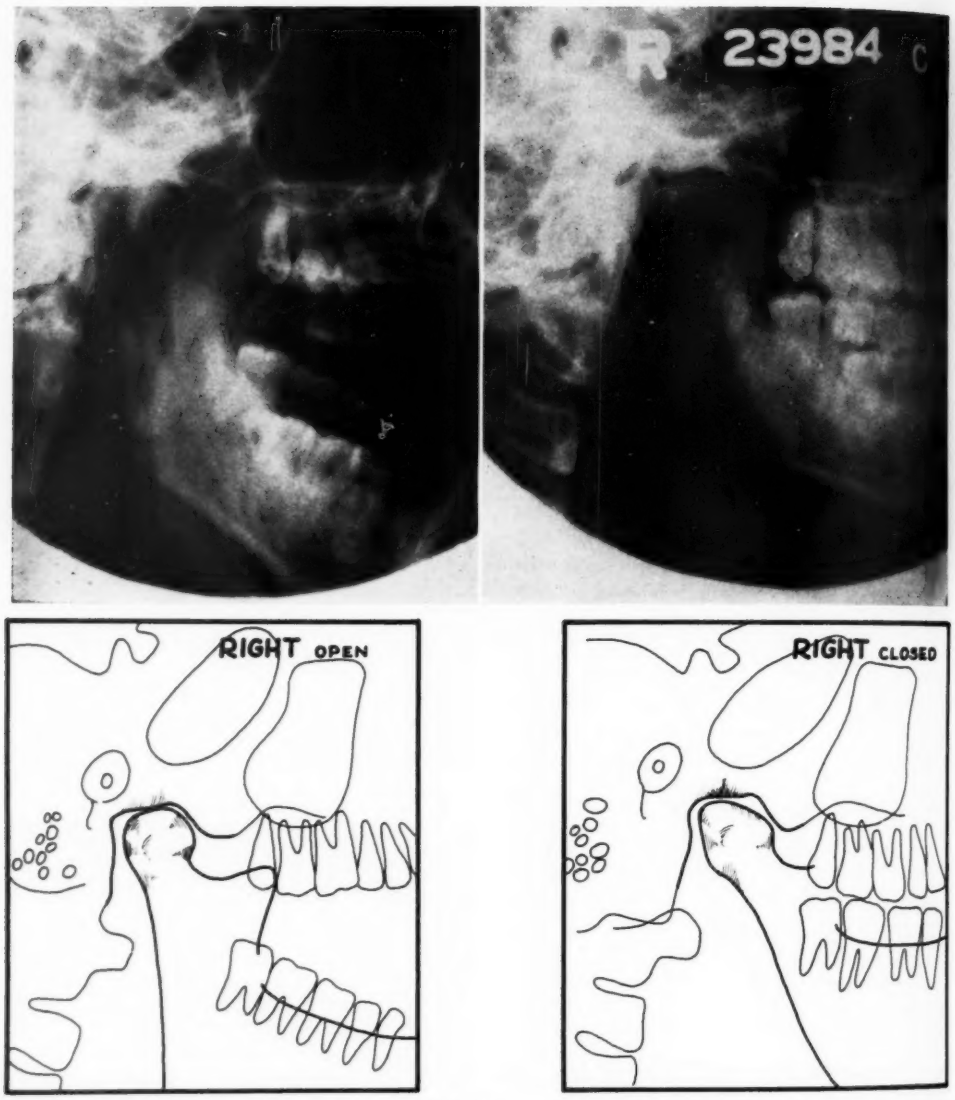

Fig. 3. Open- and closed-mouth views of right temporomandibular joint, with artist's sketch of salient features. Note the bulbous enlargement of the mandibular condyle, which fails to move forward on the eminence in the open-mouth view.

dyle may be secondary to infection in the middle ear or temporomandibular joint. There have been attempts to explain the etiology on a histopathological basis. Rushton (6) reported a case in a 28-year-old soldier with both cartilaginous formation and osteogenesis proceeding actively. There was no closing plate of bone, which should have appeared about ten years before. The combined thickness of the precartilaginous and cartilaginous layers was greatly increased, exceeding in places that which is normal at birth. Thoma states that in few of the reported cases in which surgical excision was done could any microscopic abnormalities be found in either the bone or bone marrow of the excised part (7).

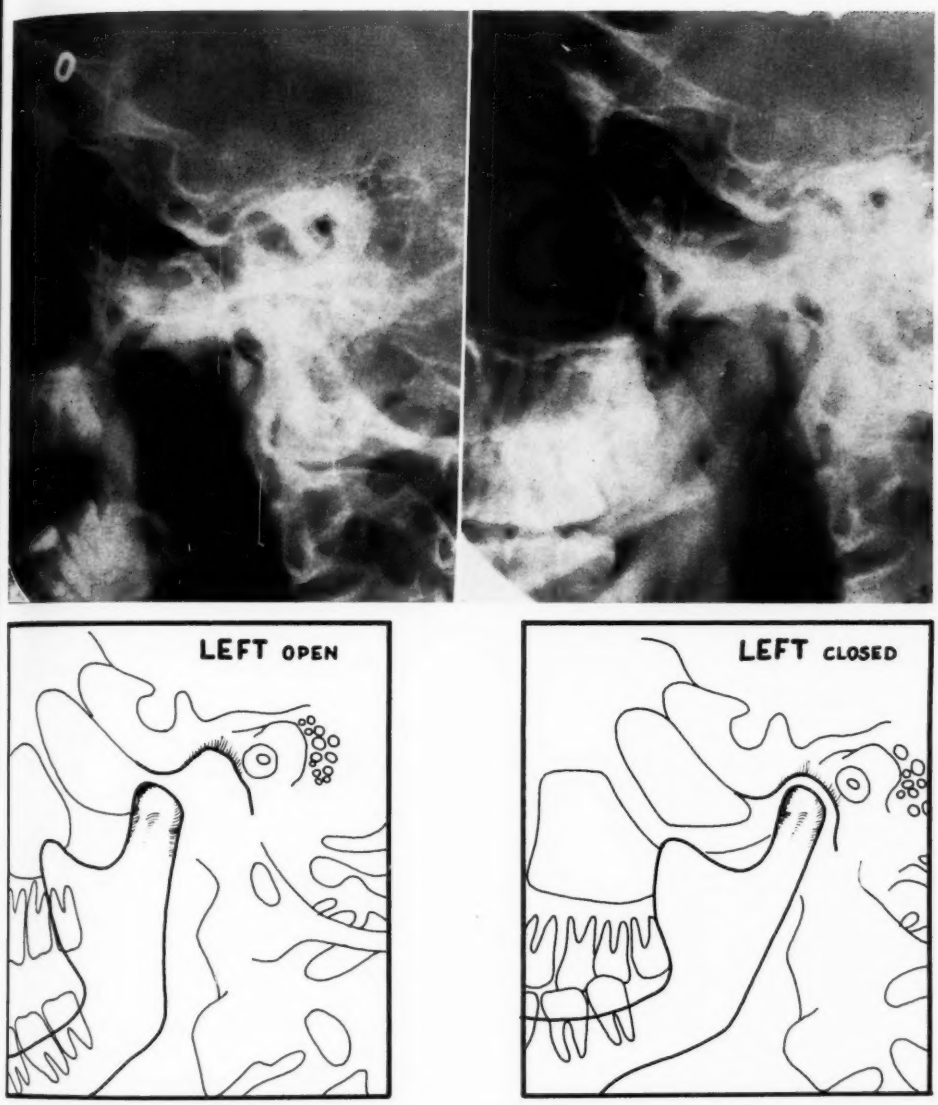

Fig. 4. Open- and closed-mouth views of left temporomandibular joint, with artist's sketch. The findings are normal.

CASE REPORT

J. P. A., a 31-year-old farmer, was first seen on Nov. 24, 1958, with swelling of the left side of the jaw. This had been slowly increasing during the preceding two years and was almost entirely asymptomatic. The only reason for seeking advice was the facial deformity, which was becoming increasingly obvious. On further inquiry, the patient admitted that he had noticed a separation of the teeth on the right side of the jaw, to the extent that most of his chewing was done on the left, and also that wide opening of the mouth caused a cracking noise on the right side. He had always enjoyed good health, with no unusual dental problems. There was no history of injury to the jaws at any time. The family history and functional inquiry were noncontributory.

Physical examination showed the abnormalities to be confined to the mouth and jaws. The facial deformity was obvious, characterized by flattening of the right side of the face and an apparent protrusion of the left side of the jaw toward the left

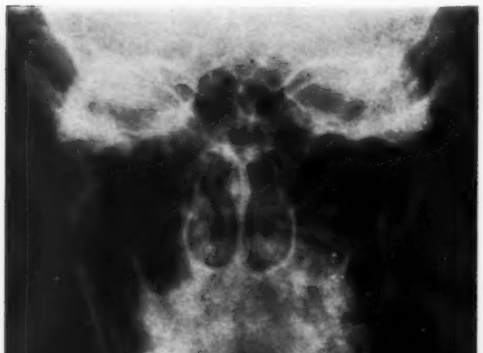

Fig. 5. Postero-anterior view of the mandible, showing asymmetry and elongation of the vertical ramus on the right side.

(Fig. 1). This was more apparent than real and was found to be due to an increase in length of the ascending ramus on the right side of the mandible. The distance between the condyle and mandibular angle, clinically, was 68 mm. on the left as compared to 82 mm. on the right. The patient's bite was found to be open on the right side, with no contact of teeth from the right molar area to the left cuspid region (Fig. 2). There was no limitation of motion in the left temporomandibular joint, but the right condyle had no anterior excursion and merely moved laterally toward the cheek when the mouth was widely opened. This condyle was clinically palpable and distinctly larger than that on the left.

Roentgenograms of both temporomandibular joints, with the mouth open and closed, showed a normal appearing condyle on the left side, which moved forward on the eminence in the open-mouth view. On the right side, the condyle was grossly enlarged and bulbous in appearance, and, in the open-mouth view, failed to show normal forward motion (Fig. 3). On the left side, the temporomandibular joint was normal (Fig. 4). The asymmetry of the mandibles was most apparent in the postero-anterior projection (Fig. 5). The vertical ramus of the right mandible was elongated and by direct measurement was 1.2 cm. longer than that on the left. The final impression was hypertrophy of the right mandibular condyle and elongation of

Fig. 6. Operative specimen showing bulbous enlargement of the condyle. The histologic finding was benign osseous hyperplasia.

the vertical ramus of the right mandible, resulting in asymmetry and deformity of the lower jaw.

On April 2, 1959, the right condyle was removed through a preauricular approach. The specimen (Fig. 6) showed gross deformity of the entire head of the condyle with enlargement in all dimensions. Microscopically the findings were consistent with benign osseous hyperplasia. Postoperative recovery was uneventful. Rubber-band intermaxillary traction was utilized for three weeks for partial immobilization and stabilization of the mandible. The patient was then able to use both sides of the mouth for mastication, whereas prior to surgery he could chew only on the left. His facial asymmetry was partially corrected. The open-bite deformity between the anterior teeth was still present but was less marked than preoperatively.

A review of the literature revealed condylar hyperplasia to be well known in European surgical clinics but Anglo-American authors consider it to be rare (3, 7, 9). Gottlieb (2) states that there are presumably numerous mild cases which go unnoticed by the patient or doctor. The apparent rarity of the condition is blamed on the fact that only a few patients seek treatment.

In 1946, Rushton (6) surveyed the literature and reported 29 cases, including 3 of his own. Up until 1956, there were fewer than 50 cases on record (4), with none in the radiographic literature. The first case was described in 1836, when Adams (1) interpreted a monstrous enlargement of the mandibular condyle as rheumatoid arthritis. In several of

Thoma's (7) cases, an associated underdevelopment of the coronoid process is mentioned. This is an inconstant feature. Most authors urge early operative correction because of the progressive tendency of the disease. Early surgical excision of the enlarged condyle almost immediately corrects facial asymmetry and malocclusion and relieves pain when present. Thoma states that the final diagnosis of a true hyperplasia of the mandibular condyle can be made only by histologic study of the surgical specimen to rule out other simulating causes, as Paget's disease, fibrous dysplasia, osteoid osteoma, chondroma, giant-cell tumor, and osteogenic sarcoma.

SUMMARY

A proved case of hypertrophy of the right mandibular condyle with elongation of the vertical ramus of the right mandible, causing asymmetry of the face and malocclusion, is reported. Some of the etiologic aspects are discussed along with the major roentgenologic criteria necessary to establish the diagnosis. The literature is reviewed, indicating the relative rarity of the entity.

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SUMMARIO IN INTERLINGUA

Hypertrophia Unilateral del Condylo Mandibular

Hypertrophia unilateral del condylo mandibular es un entitate rar de etiologia obscur, causante deformitate facial e malocclusion. Le roentgenogrammas es characteristic. Le allargamento del capite del condylo, associate con elongation del ramo ascendente del mandibula, causa un abassamento del angulo mandibular e un migration del symphyse del mento verso le latere non-afficite, producente—como in le caso hic reportate—le impression de un tumor crescente al latere normal. Le tractamento consiste in le precoce excision del allargate condylo. Isto corrige quasi immediatemente le asymmetria facial e le malocclusion e allevia le dolores, si tales es presente.

Es reportate un caso in que le operation resultava in un correction partial del deformitate. Le constatationes microscopic esseva compatibile con benigne hyperplasia ossee.

Myelographic Identification of the Dentate Ligament[1]

PAUL TENG, M.D.

THE DENTATE ligament is a thin fibrous band situated on either side of the spinal cord. It separates the anterior from the posterior nerve roots. Its inner border is continuous with the pia mater and its lateral border is fixed at intervals to the dura mater by 21 triangular processes on each side. The first of these is attached to the dura mater opposite the margin of the foramen magnum, between the vertebral artery and the hypoglossal nerve, and the last near the lower end of the spinal cord at the level of D-12 or L-1. The lower end of the dentate ligament terminates in a two-pronged fork, the lateral prong forming the last dentate digit and the medial prong being prolonged along the side of the conus medullaris. The ligament is thicker in its cervical than dorsal section (1).

The dentate ligament can be visualized in the lateral projection of a Pantopaque myelogram as a linear radiolucent shadow, its anterior and posterior surfaces being outlined by the opaque substance. Its visualization is facilitated by the use of at least 10 c.c. of the medium and a lateral projection. Because of its greater thickness, the cervical dentate ligament is more readily visualized than the dorsal portion.

At times, the dentate ligament is not visualized as a linear radiolucent shadow (Figs. 1 and 2) but is indicated by a dense radiopaque column (Fig. 3), the posterior border of which outlines the dentate ligament as a result of collection of Pantopaque under its ventral surface. The dentate ligament has been visualized in 10 out of 23 lateral projections in 36 cervical myelograms, and 4 dorsal myelographic studies.

The above interpretation of the linear radiolucent shadow on the lateral myelogram as the dentate ligament has been

Fig. 1. Cervical myelogram, lateral projection. Linear radiolucent shadow indicates dentate ligament.

proved on cervical myelograms of fresh cadavers. In 5 fresh cadavers a laminectomy of the cervicodorsal spine was performed in prone position. The dura was opened along its midline posterior aspect from C-5 to D-2. The dentate ligaments were identified and silver clips were applied to the edge. In 2 instances, the clips were applied to the dentate ligament on both sides. A No. 14 rubber catheter was passed into the subarachnoid space with its tip placed at C-3. The dura was closed with interrupted stitches and water was injected through the catheter to refill the subarachnoid space in order to reproduce a condition simulating "normal" anatomical circumstance. After the arachnoid space had been filled with water,

[1] From the Neurological Service, Kaiser Foundation Hospital, Los Angeles, Calif. Accepted for publication in September 1959.

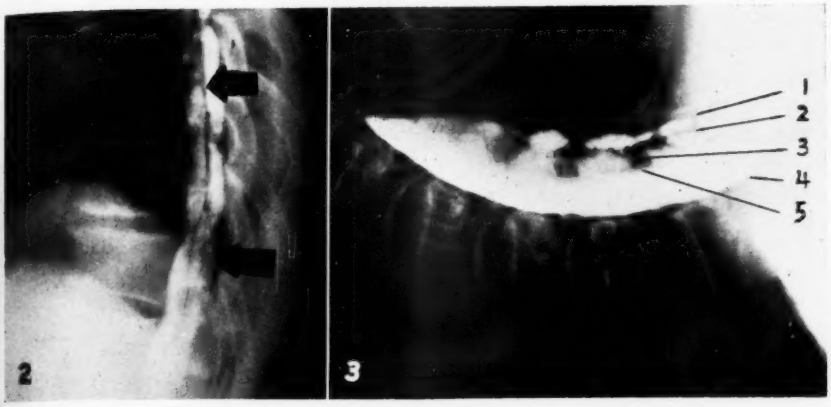

Fig. 2. Dorsal myelogram. Arrows indicate dentate ligaments of the dorsal area.
Fig. 3. Opaque line indicates dentate ligament. 1. Posterior dural wall. 2. Posterior surface of cord. 3. Posterior rootlets visualized as radiolucent oblique streaks. 4. Ventral dural wall. 5. Dentate ligament.

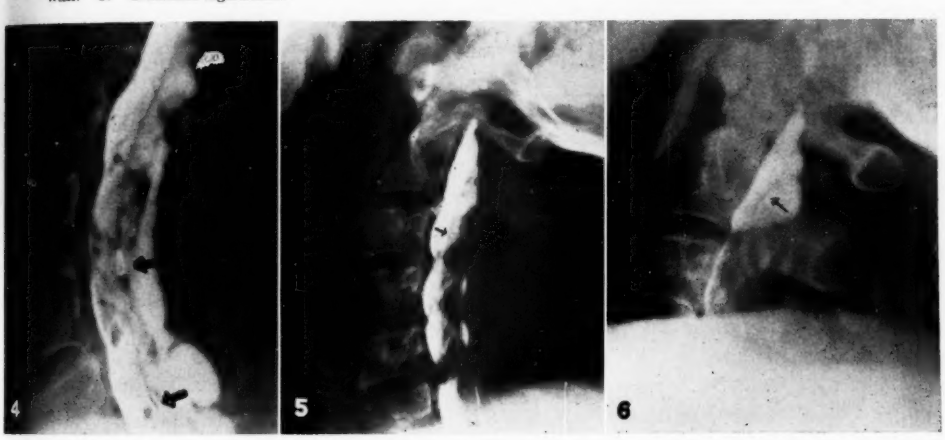

Fig. 4. Cervical myelogram in a cadaver. Arrows indicate silver clips applied to the dentate ligament. The clips may be seen in continuity with shadows of the dentate ligament.
Fig. 5. Arrow indicates dentate ligament. Note interruption of dental ligament line at C 4-5 and C 5-6 in spondylosis.
Fig. 6. Intramedullary hemangioma, C 2-6. Arrow indicates markedly depressed dentate ligament.

10 c.c. of Pantopaque was instilled through the catheter. Air bubbles were led out from the subarachnoid space by manipulation of the neck and during the slow withdrawal of the catheter. The neck of the cadaver was placed in hyperextension and a roentgenogram was obtained in lateral projection. The silver clips were visualized in each instance in line with the radiolucent streak, the dentate ligament (Fig. 4).

In cervical spondylosis with osteophytic ridges, the myelographic continuity of the dentate ligament may be disrupted (Fig. 5). This has been observed in 4 of 20 surgically treated cases of cervical spondylosis with nerve roots and or spinal cord compression.

In intradural neoplasm, the dentate ligament may be depressed or displaced ventrally, if the lesion is posteriorly situated. Figure 6 is a myelogram of a thirty-one-year-old patient who had an intradural and intramedullary hemangioma extending from C-2 to C-6. The spinal cord was hugely distended, to about 1

inch in width. The figure shows the rostral end of the tumor, and the dentate ligament is seen curving ventrally. At operation, the tumor was found involving mainly the posterior portion of the spinal cord.

SUMMARY

The dentate ligament can be visualized in the Pantopaque myelogram. In the lateral projection it is identified as a linear radiolucent shadow outlined by the opaque medium on its ventral and posterior surfaces.

In cervical osteospondylosis, the myelographic continuity of the dentate ligament may be disrupted.

In the presence of an intradural neoplasm, the dentate ligament may be displaced. The direction of its displacement may be indicative of the location of the tumor in the ventral or posterior aspect of the cord. On this point further investigation is needed.

4867 Sunset Blvd.
Los Angeles 27, Calif.

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SUMMARIO IN INTERLINGUA

Identification Myelographic del Ligamento Dentate

Le ligamento dentate pote esser visualisate in le myelogramma a Pantopaque. Illo es identificate, in un exposition lateral, como un radiolucente umbra linear, delineate per le medio opac al superficies ventral e posterior.

In le presentia de un neoplasma intradural, le ligamento dentate pote esser displaciate. Le direction del displaciamento pote esser un indication del sito del tumor in le aspecto ventral o posterior del medulla spinal. Investigationes additional es requirite relative a iste puncto.

In osteospondylosis cervical, le continuitate myelographic del ligamento dentate pote esser disrupte.

Double-Contrast Angiocardiography

An Experimental Method for Demonstrating Surgically Created Interatrial Septal Defects in Dogs[1]

JAMES F. MARTIN, M.D., JESSE R. MEREDITH, M.D., and FRANK R. JOHNSTON, M.D.

VENOUS angiocardiography with liquid opaque medium has been generally unsuccessful in demonstrating atrial septal defects in infants, children, and adults (3). Sporadic reports of success with this method have appeared, but the experience has been so inconstant that the procedure has not been recommended for the diagnosis of this abnormality. Kjellberg *et al.* (4), in discussing angiocardiography in the diagnosis of atrial septal defect, state that, in their opinion, "the results of examination with intravenous injection of the contrast medium do not warrant further attempts with the technique." The present report is concerned with our experience in demonstrating such defects in dogs by the simultaneous intravenous injection of an opaque medium and 100 per cent carbon dioxide.

The method of study employed was devised after the observation of results obtained by the intracardiac injection of pure carbon dioxide, as described by Stauffer *et al.* (5–7, 9). These investigators obtained satisfactory visualization of the anatomy of the chambers of the heart and great vessels with this medium and cineradiography. Their experience showed this to be a relatively safe procedure in dogs, even when the carbon dioxide was injected *via* catheter into the chambers of the left side of the heart. Carbon dioxide in amounts as great as 7.5 c.c./kg. appeared to be well tolerated by dogs and to be absorbed rapidly in the blood stream. Limited human application was also observed without incident (2). Recently, these workers have described the visualization of an atrial septal defect in dogs by this method (5, 6) but they failed to demonstrate the defect in two patients (10). As much as 11 liters of pure carbon dioxide have been injected intravenously within a five-minute period in a dog without sequelae (8).

A double-contrast technic employing carbon dioxide and Diodrast has been described by Durant *et al.* (2). It has provided better visualization but results in a marked depressing effect on the heart which is not noted when carbon dioxide is used alone. Recent experimental work with this method has been reported by Blickman (1).

METHOD

Thirty studies were performed on 9 normal dogs and 5 with surgically created atrial septal defects. The margins of the defect were marked with metal clips in one dog. The radiographs were made with the Schönander biplane rapid film-changing device at a speed of four per second and cineradiography (not demonstrated here) using 32 frames per second. Comparison studies were done in the prone and supine positions during the intravenous injection of a liquid opaque medium, carbon dioxide, and a combination of the two injected simultaneously.

OBSERVATIONS

Position of the Left Atrium: The left atrium was outlined in one normal dog by surgical insertion of a catheter *via* thoracotomy and the injection of 50 c.c. of carbon dioxide. Simultaneously, opaque medium was injected into a jugular vein. The anatomical location of the left atrium was established and served as a pattern to verify the demonstration of a septal defect

[1] From the Departments of Radiology and Surgery of the Bowman Gray School of Medicine of Wake Forest College, and the North Carolina Baptist Hospital, Winston-Salem, N. C. Accepted for publication in September 1959.

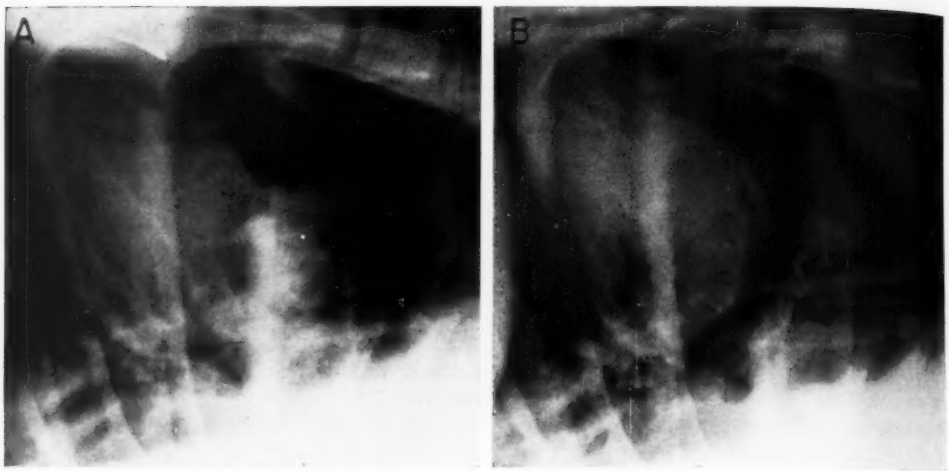


Fig. 1. Normal dog in supine position; 50 c.c. of 100 per cent carbon dioxide has been injected into the left jugular vein.
A. The right atrium and ventricle are visualized and the thickness of the ventricular wall is demonstrated.
B. The pulmonary artery and valves are demonstrated.

by the intravenous injection of pure carbon dioxide. The left atrium occupies a more dorsal position than does the right (Fig. 3).

Contrast Studies in Normal Dogs: The initial studies were performed with carbon dioxide on the normal dog in the supine (Fig. 1) and prone (Fig. 2) positions, for purposes of comparison. The anterior portion of the right ventricle appeared well outlined with the dog in the supine position, and the prone position permitted visualization of the posterior portion. The pulmonary artery, pulmonary valve, and the tricuspid valve appeared to be best demonstrated in the supine position. The gas appeared to be eliminated in the lungs, and no visualization of the left side of the heart was obtained.

The double-contrast studies, *i.e.*, the simultaneous injection of opaque medium and carbon dioxide, were carried out to compare the flow of these substances within the heart during the cardiac cycle. It was observed that the opaque medium followed the flow of the blood, while the carbon dioxide remained temporarily

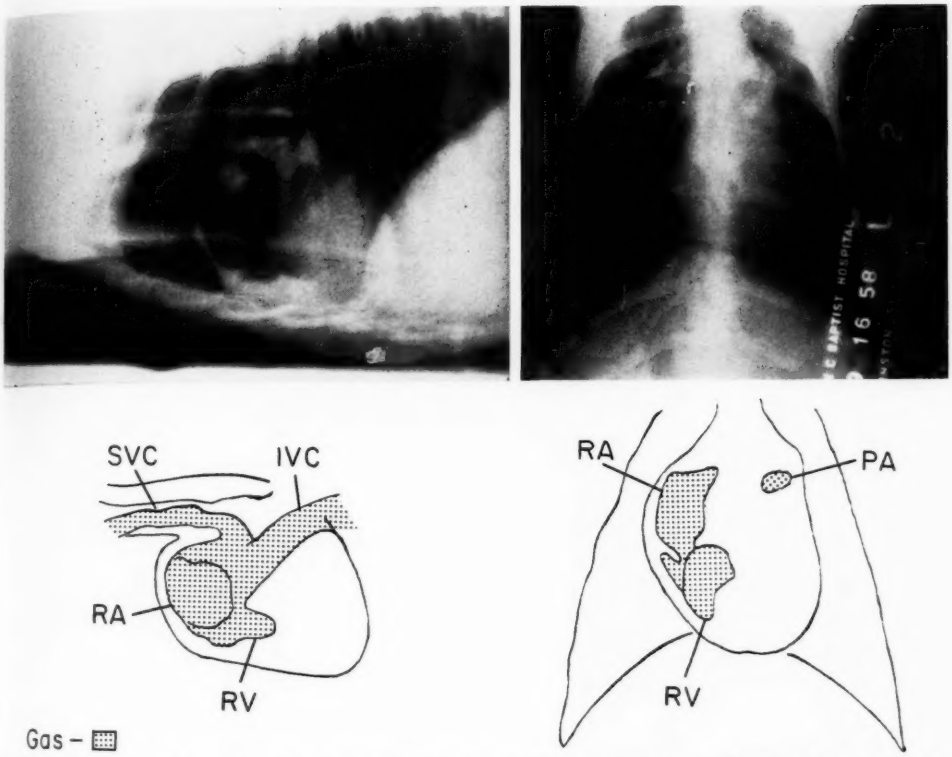


Fig. 2. Normal dog in prone position: film studies made after the injection of 50 c.c. of pure carbon dioxide into the jugular vein. The superior and inferior vena cava are well outlined. The right atrium and ventricle are also filled, with the ventricle in systole. The pulmonary artery contains only a small amount of carbon dioxide.

within the right side of the heart and pulmonary vessels until it was dissolved.

Contrast Studies in Dogs with Surgically Created Atrial Defects: Multiple studies were performed on the dogs with surgically created atrial defects. These included routine venous angiocardiograms with a liquid opaque medium (Fig. 4), carbon dioxide injections (Fig. 5), and a double-contrast study using a combination of the two (Figs. 6 and 7). These were carried out in both the prone and supine positions.

The routine venous angiocardiogram obtained with the opaque medium was similar to that in the normal dogs. There was no evidence of passage of the medium from the right to the left atrium in the early phase of the cycle. No significant re-opacification of the right atrium could be detected (Fig. 4). The position of the dog had no apparent influence on the results.

The studies with intravenous carbon dioxide demonstrated an immediate passage of the gas from the right to the left atrium in the prone (Fig. 5) but not in the supine position. In the lateral projection, air in the bronchial tree tended to overshadow the left atrium. Its identification was possible, however, by comparison with the scout film made prior to the injection of the gas and the use of serial film studies.

The double-contrast study, *i.e.*, the simultaneous injection of a liquid medium and carbon dioxide, provided further information and confirmed the presence of an atrial septal defect (Figs. 6 and 7). This combination permitted a demonstration of the right atrium and ventricle by the liquid opaque medium, while the gas was

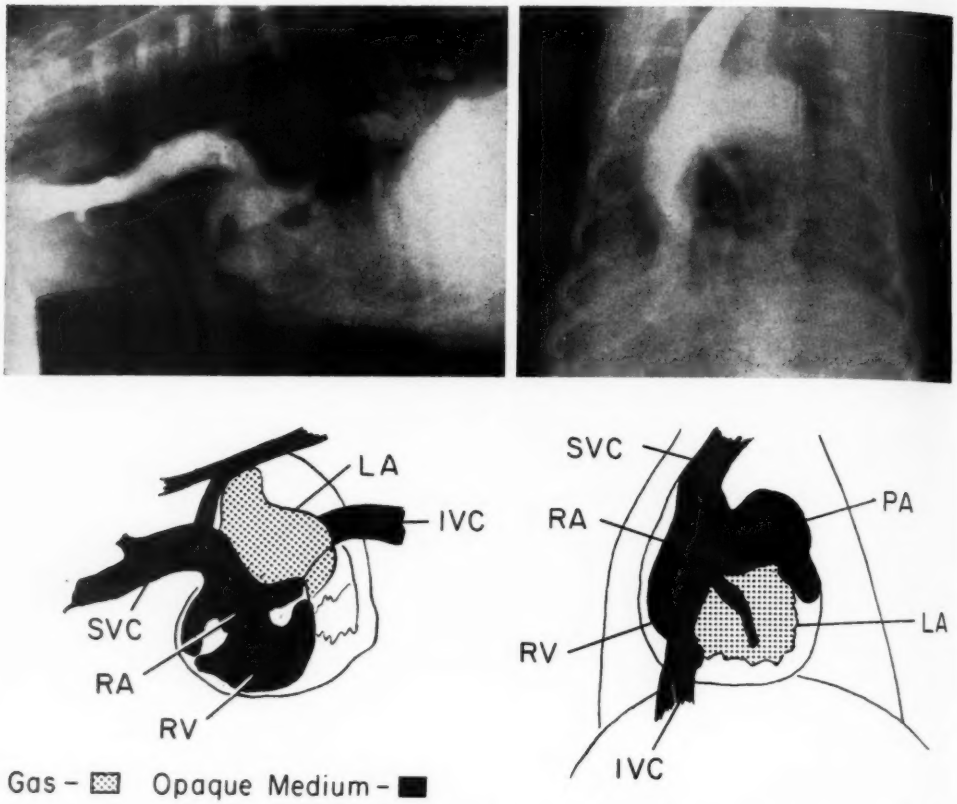
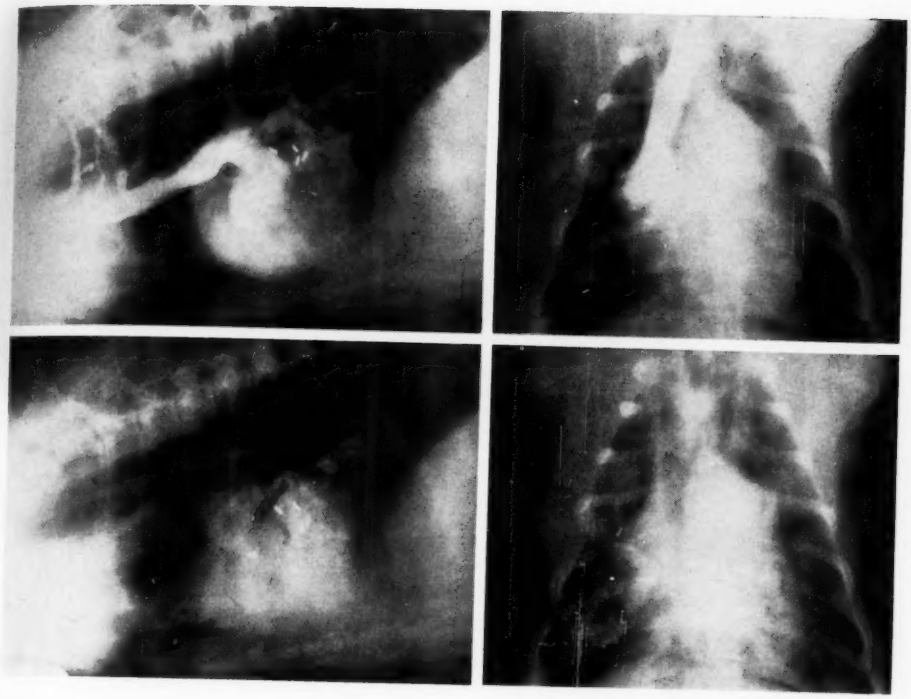


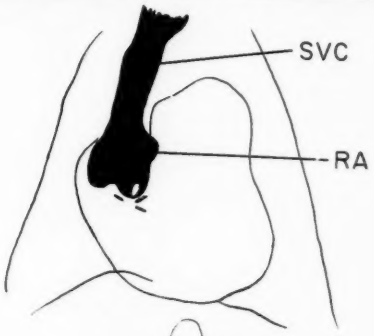
Fig. 3. Normal dog in prone position. A catheter was inserted into the left atrium *via* thoracotomy. Simultaneously 50 c.c. of carbon dioxide was injected through the catheter into the left atrium and 20 c.c. of liquid opaque medium into the external jugular vein. The study demonstrates the relative positions of the right and left atrium, each filled with a different medium.

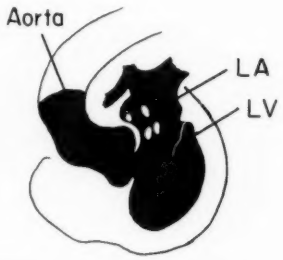
identified in the right as well as in the left atrium, having passed through the atrial defect. Later in the cycle, the liquid medium was identified in the left atrium along with the gas (Fig. 6, B). Thus, the liquid medium served to demonstrate the location of the chambers and the gas showed the presence of an atrial septal defect.

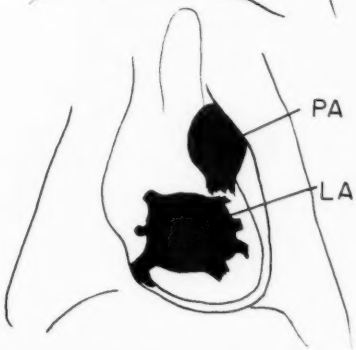
DISCUSSION

The utilization of combined pure carbon dioxide and an opaque medium appears to offer further possibilities in the study of intracardiac shunts. The liquid medium followed the course of the blood and outlined the chambers and vessels in the cardiac and pulmonary circulation. The course of the gaseous medium was not shown, but observation suggests that it is determined by the simple physical fact of a gas being less dense than a liquid and by the relative position of the cardiac chambers in various positions. The gas seeks the uppermost part of the chamber or chambers, and the liquid the more dependent part. This difference in the passage of carbon dioxide and opaque medium through the heart affords an opportunity to visualize the flow of blood through the heart and also demonstrates the advantage of the physical properties of the gas in consistently revealing an intracardiac defect. The valve may also be shown and it may appear incompetent to gas. The inertia of the leaflets is great relative to the









Opaque Medium – ■

Fig. 4. Dog with an interatrial septal defect marked with metal clips, in prone position. Routine angiocardiogram with liquid opaque medium. Normal flow through the heart is demonstrated without detectable evidence of reopacification of the right atrium.

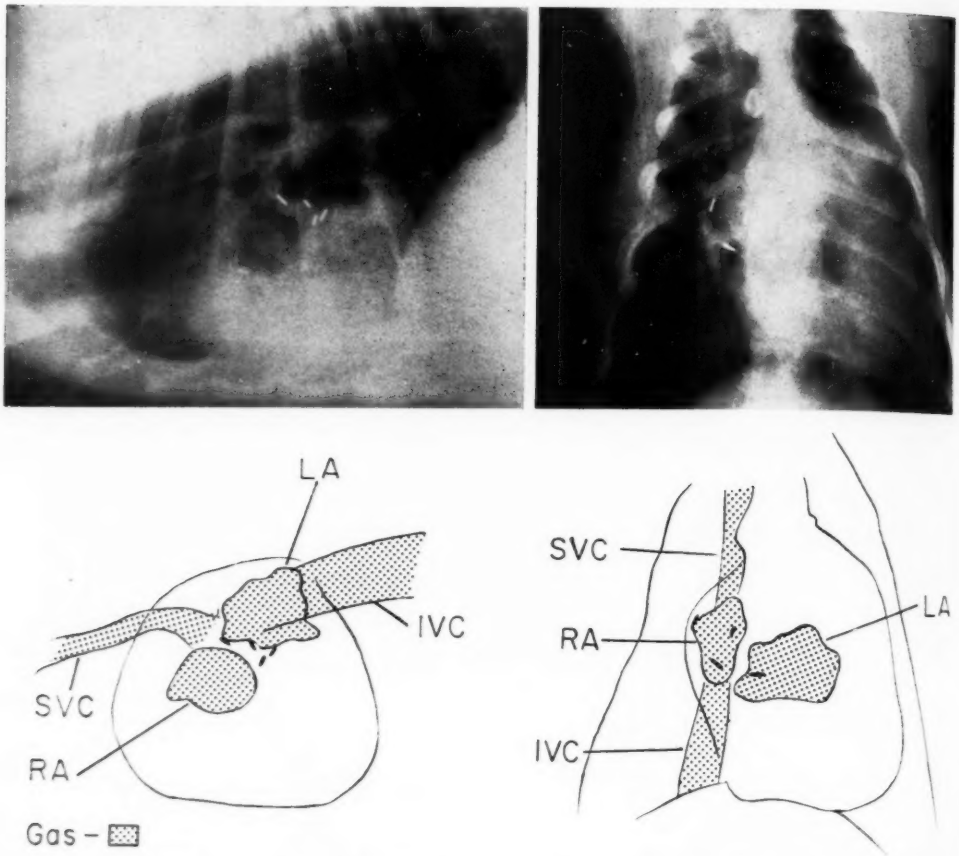


Fig. 5. Dog with interatrial septal defect marked with metal clips, in prone position; 50 c.c. of 100 per cent carbon dioxide has been injected intravenously. The film series shows the gas to be within the right atrium and left atrium immediately following the injection. A separation of the two chambers is seen and is marked by metal clips placed on the interatrial septal defect.

gas, and regurgitation occurs, producing a bolus and repeated visualization of the chamber. The additional effect of the compressibility of a gas in relation to its passage through a heart valve or shunt during the variations in pressure occurring in the cardiac cycle remains to be determined. The gas appeared to pass rapidly through the right atrium and the atrial defect in the prone position. Studies in the supine position were much less satisfactory in the demonstration of the defect. The relative positions of the atria in the prone position appeared to be the most important factor in the passage of the gas from the right to the left atrium.

Some studies demonstrated the gas and opaque medium mixed within the main pulmonary artery and its secondary branches, producing a double-contrast appearance within them? This observation suggests the possibility of further development of this technic in the study of disease of the pulmonary arteries. The gas appeared to be eliminated in passage through the pulmonary capillaries and arterioles, since it was not seen in the large pulmonary veins.

The opaque medium was useful (in the study) in identifying the position of the atria, especially the left. The gas passed through the defect and remained in the

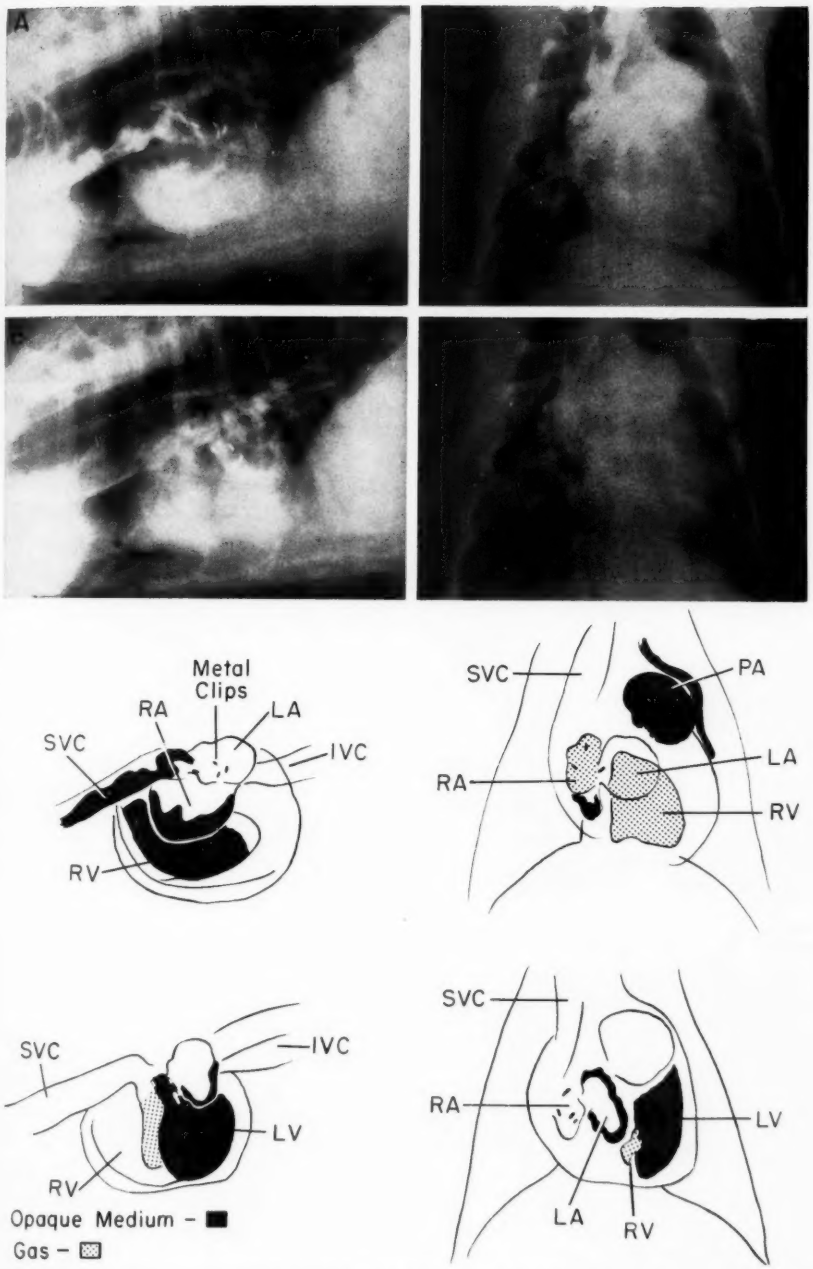


Fig. 6. Dog with interatrial septal defect marked by metal clips, in the prone position. Double contrast angiocardiogram obtained with 50 c.c. of 100 per cent carbon dioxide and 30 c.c. of opaque medium (50 per cent Hypaque).

A. This study demonstrates visualization of the right and left atria by the carbon dioxide. The opaque m dium is seen in the superior vena cava, right atrium, and ventricle.

B. This study later in the series demonstrates carbon dioxide and some opaque medium in the left atrium. The right and left ventricles are faintly visualized with the opaque medium.

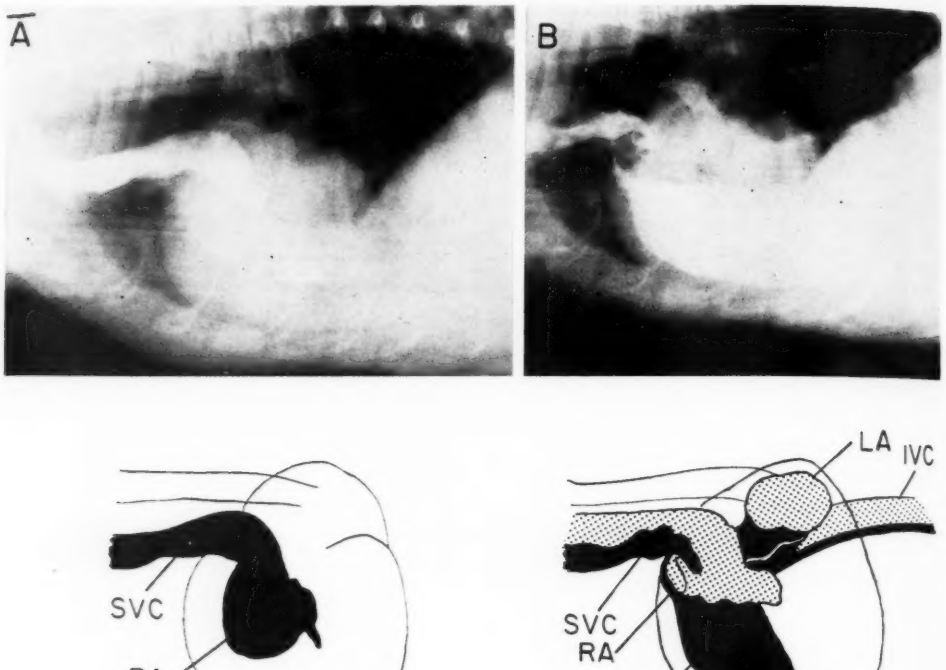


Fig. 7. Dog with interatrial septal defect, unmarked, in prone position. Double contrast angiocardiogram obtained with 50 c.c. of 100 per cent carbon dioxide and 30 c.c. of Hypaque (50 per cent).

A. The studies made in the lateral projection demonstrate early filling of the vena cava and right atrium, by opaque medium, on the initial film study.

B. The carbon dioxide was injected shortly thereafter and demonstrates the presence of gas in the left atrium, with rapid passage through the interatrial septal defect.

left atrium for several seconds. Before the gas was absorbed, the opaque medium had passed through the pulmonary vessels and also entered the left atrium (Fig. 6, B). This phase of the study thus demonstrated both media within the left atrium and the opaque material helped further to verify the presence of the gas within this chamber. But while the opaque medium served a useful purpose in this study it is probably not essential to diagnosis. It was not useful in demonstrating the presence of the defect. Further experience and observation of the appearance and behavior of the gas in the heart will undoubtedly prove the value of this medium alone.

Attempts were made to inject both media simultaneously through different veins, as rapidly as possible. An automatic injection device was used with the liquid medium in some instances but did not appear to be a requirement in the study. The carbon dioxide was injected manually. It was not possible to obtain an exact simultaneous injection and in some instances the gas appeared in the right atrium before the opaque medium. The most satisfactory studies were those in which the opaque medium was introduced slightly ahead of the carbon dioxide (Fig. 7, B).

The present studies were made with a rapid changer device and with cineradiography. The radiographs were obtained at a speed of four per second and demonstrate the various phases of systole and

diastole in the cardiac cycle. The device, however, is not indispensable in diagnosis by this method, for the gas persists in both atria for several seconds before being absorbed. Cineradiography demonstrates the behavior of gas within the heart chambers but otherwise is probably not essential.

CONCLUSIONS

1. The chambers of the normal dog's heart and those with surgically created atrial septal defects were visualized with the aid of intravenous injection of a liquid opaque medium, 100 per cent carbon dioxide, and a combination of the two.

2. Venous angiocardiography in dogs with surgically created atrial defects demonstrated no evidence of passage of the liquid opaque medium from the right to the left atrium.

3. With double-contrast study the opaque medium was seen to pass through the heart chambers and pulmonary vessels in a normal fashion, while the carbon dioxide passed through the atrial defect from the right to the left atrium.

4. The use of intravenous carbon dioxide with or without an opaque medium appears to open a new avenue in the definitive diagnosis of septal defects. Intravenous carbon dioxide alone appeared to demonstrate the atrial defect adequately in the prone position.

5. There were no adverse reactions encountered to the intravenous injection of 100 per cent carbon dioxide.

NOTE: The authors wish to express their appreciation to Winthrop Laboratories for providing the Hypaque used in this study.

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Winston-Salem, N. C.

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SUMMARIO IN INTERLINGUA

Angiocardiographia a Duple Substantia de Contrasto: Studios Experimental

In canes con chirurgicamente create defectos atrial, angiocardiographia produceva nulle evidentia de un passage del medio ab le atrio dextere al atrio sinistre. Tamen, in studios a duple substantia de contrasto—utilisante un liquide substantia de contrasto e bioxydo de carbon—le medio opac passava normalmente per le cameras cardiac e le vasos pulmonar, durante que le bioxydo de carbon passava per le defecto al atrio sinistre.

Le uso de intravenose bioxydo de carbon, con o sin un substantia opac, pare aperir nove vias pro le diagnose definitive de defectos septal. In decubito ventral, intravenose bioxydo de carbon per se pareva capace a demonstrar le defecto atrial adequatemente.

Tissue Oxygen Tension and Radiotherapy

A Review and Bibliography Based on a Conference in Burlington, Vermont, August 1958[1]

P. HOWARD-FLANDERS, and O. C. A. SCOTT[2]

THE radiosensitivity of tissues depends upon various factors, important among which is the oxygen tension. It has generally been found that tissues are two or three times less radiosensitive when anoxic. In certain malignant growths, moreover, there is a tendency toward the occurrence of areas of low oxygen tension, with, presumably, a reduced sensitivity to radiation. The realization that tissue oxygen tension may be of fundamental importance in radiotherapy has stimulated research in many directions. Various aspects of this subject were discussed at an interdisciplinary conference held in Burlington, Vermont, in August 1958, sponsored by the Radiation Study Section of the National Institutes of Health, under the chairmanship of Dr. Howard J. Curtis. Physiologists, radiobiologists, radiologists, and pathologists who had been working in fields related to this problem were in attendance.

RADIOBIOLOGICAL CONSIDERATIONS

Introducing the subject, *L. H. Gray* referred to the first demonstration by Hollcroft, Lorenz, and Matthews (1) that a mouse lymphosarcoma can be sensitized by placing the animal in oxygen with 5 per cent carbon dioxide during irradiation. The relation between oxygen tension and radiosensitivity has been tested in a variety of organisms, tumour cells, plants, insects, and micro-organisms, with results which are striking in their similarity (2). Cells from all these organisms are less sensitive to x-rays by a factor between 2 and 3 when they are anoxic. In the Ehrlich mouse ascites tumour, for example, this ratio is close to 3, as judged from the doses required to induce chromosome aberrations in 50 per cent of the cells fourteen hours after inoculation (3). The ratio appears to be independent of temperature.

The switch in sensitivity following a change in oxygen tension is very rapid indeed, being certainly less than two seconds in the ascites tumour (4) and less than one-fiftieth of a second in bacteria (5). As the oxygen concentration is increased from zero, the radiosensitivity increases rapidly, but it reaches a plateau beyond which there is very little increase even at the highest concentrations. The oxygen concentration required to raise the sensitivity halfway toward the maximum may be called the critical oxygen concentration. Cells with rather less than the critical concentration are relatively insensitive to radiation, while cells with rather more than that amount will be nearly as sensitive as fully oxygenated cells. The critical oxygen tension for Ehrlich mouse ascites tumour cells *in vitro* is about 2 mm. Hg at 18° C. and a little higher at 37° C. (3).

Gray referred to measurements of the sensitivity to x-rays which have been made on mammalian cells from various sources. With human carcinoma cells cultured *in vitro* under conditions in which single cells will grow and form clones, Puck and Marcus (6) have shown that the 37 per cent survival dose for aerobic cells, corrected for photoelectrons from the glass surface, is close to 140 rads (7).

Hewitt (8, 9) obtained survival curves with a mouse leukemia 2 or 3 cells of which injected into the peritoneum will kill 50 per cent of the mice within forty days.

[1] Accepted for publication in September 1959.

[2] Medical Research Council, Experimental Radiopathology Research Unit, Hammersmith Hospital, London, W. 12, England. Present address: Yale University School of Medicine, New Haven, Conn.

[3] British Empire Cancer Campaign, Research Unit in Radiobiology, Mount Vernon Hospital, Northwood, Middlesex, England.

The tumour-bearing animal is given whole-body irradiation and killed immediately thereafter so that the tumour can be harvested. Tumour cells are then counted and diluted *in vitro* before injection into new hosts. Exponential survival curves have been obtained which extend down to a surviving fraction of 10^{-5}, the slope of which indicates that the 37 per cent survival dose is 165 rads. If one assumes that the oxygen effect of 3 : 1, observed with small doses, is applicable at all dose levels, it is not difficult to calculate the size of the cell populations which will be killed by a given dose of x-irradiation.

The Initial Numbers of Cells for Which There is a 90 per cent Chance that None Will Survive a Single Dose of 4,500 rads, Assuming D_{37} = 150 rads and that Anoxia Gives Threefold Protection

Tissue oxygen tension mm. Hg	0	1	4	100
Initial numbers of cells	2×10^3	3×10^5	5×10^7	10^{12}

Since a tumour large enough to be diagnosed clinically will probably contain between 10^7 and 10^{11} cells, it appears that the aerobic cells should be inactivated by 4,500 rads, but that there may be some survivors from any zone of more than 10^4 cells which are anoxic. This number of cells (10^4) will occupy a volume about the size of a pinhead. The problem is how to overcome this adverse situation.

Two methods have been discussed. Either the pressure of oxygen in the respired gas can be increased or, alternatively, all the tissues in the irradiated zone may be made anoxic. Thus each cell might assume its maximum sensitivity in high-pressure oxygen, or its minimum sensitivity when anoxic. In either event, it should be possible to avoid the unfavorable situation in which only the sensitivity of the tumour cells is depressed.

M. Ebert reported experiments on the action of high-pressure gases in reducing the radiosensitivity of aerated *Vicia faba* roots to the anoxic level. The pressures of gases (in atmospheres) required for half effect are as follows: H_2, 55; He, 55; N_2, 12.5; A, 2; Kr, 2; and Xe, 1.1. All these experiments were carried out in the presence of 160 mm. Hg of oxygen (10). A reduction in the radiosensitivity of mouse ascites tumour cells in 160 mm. Hg oxygen has also been noted when the cells are irradiated *in vitro* with 600 mm. Hg nitrous oxide in place of nitrogen (11). There is considerable interest in this latter result for, should similar results be obtained following *in vivo* irradiation, it would appear that the disadvantages of the oxygen effect might be overcome if nitrous oxide were administered at atmospheric pressure.[4]

E. A. Wright reported other experiments in which argon at 50 atmospheres was found not to affect the sensitivity of excised mouse tail in 160 mm. Hg of oxygen. Moreover, argon at 5 atmospheres did not affect the sensitivity of the thymus of mice breathing 160 mm. Hg of oxygen. It is not clear whether the admixture of other gases such as nitrous oxide may be useful clinically.

TUMOUR MORPHOLOGY AND CIRCULATION

R. H. Thomlinson discussed oxygen supply in tumours where conditions of disordered circulation are frequently found. The oxygenation of particular cells is dependent upon the state of the capillary blood flow in the area and the diffusion conditions in the tissue. Outside the capillaries, oxygen concentration decreases as the distance from capillaries increases, roughly in proportion to the metabolic rate of the tissue, but modified by such factors as the flow of extravascular liquids and the lymphatic drainage. In histologic preparations from a variety of squamous-cell carcinomas from bronchus, skin, and cervix uteri, intact cells are not found at

[4] Subsequent to the meeting it has been found that the sensitivity of mice to the effects of whole-body irradiation is similar whether they are exposed in air or in 80 per cent nitrous oxide and 20 per cent oxygen (12, 13). In similar experiments in which the mice are breathing 90 per cent nitrous oxide and 10 per cent oxygen, the degree of protection obtained is not significantly greater than that due to the reduced oxygen pressure (14, 15). Moreover, nitrous oxide does not influence the radiosensitivity of mouse skin as judged by epilation (16). The protective effect is evidently found under particular conditions of experiment only.

distances greater from capillaries than 200 μ, and frequently clear lines of transition from intact to necrotic cells occur at about 170 μ, a figure which is subject to a small correction for the shrinkage of the section. The distance of these transitions is well correlated with the distance at which oxygen concentration would reach zero in a metabolizing tissue in the presence of normal capillary circulation (17).

However, similar lines of transition are often found much closer to blood vessels, so that intact cells appear to form zones of uniform width around the vessels. These zones may be as narrow as one or two cell layers. The vessel in the center of such a zone has a thin wall formed of endothelial cells and a basement membrane but is distended and congested with blood.

This pattern is of common occurrence in many forms of human cancer but is most frequently seen in human and animal sarcoma (18). Where such patterns are present in tumours, there are also oedema, haemorrhage, and general distension of blood vessels, which suggests that the circulation in these distended vessels is slower than normal and follows the same sequence of events as that which occurs in venous infarction. The mechanism of the slowing probably has a physical basis in the pressures set up as the neoplasm expands in a confined space and stretches, distorts, and compresses the tumour capsule and stroma, and especially the low-pressure systems of venules and lymphatic vessels. Such slowing will result in diminished oxygenation of the tumour and would be little affected by any dilatation of the arterioles which might result from the use of vasodilators.

X-RAY THERAPY IN HIGH-PRESSURE OXYGEN

I. Churchill-Davidson described the treatment of patients in high-pressure oxygen and the progress being made in improving the facilities. Formerly only two treatments were given, eight days apart (19). With the same apparatus, the technic has been improved so that patients are given three treatments in fifteen days and receive a total dose of 3,000 rads. No difficulty has been experienced with a total pressure of 4 atmospheres instead of the 3 formerly used. Compression is carried out in eight minutes, decompression in four. To make the best use of the oxygen, the haemoglobin concentration is raised to the normal level and care is taken to reduce risk of sepsis by means of wide-spectrum antibiotics. A total of 61 patients have been treated, of whom 28 are alive and 18 free from recurrence.

A new twin-headed cobalt unit and pressure vessel is being brought into use. This unit gives a dose rate of 70 rads per minute at the tumour and permits a drastic reduction in the time of treatment and an increase in the number of fractions to 6.

Treatment under anoxia is also being considered. One patient has been treated for an osteogenic sarcoma with a tourniquet on the leg to protect the normal tissues by anoxia. Twice the usual dose of radiation was given.

ANIMAL TUMOUR EXPERIMENTS

O. C. A. Scott discussed the problem of testing the effect of oxygen upon the treatment by x-rays of experimental tumours in animals, especially mice. There are a number of published accounts of experiments designed to test the action of oxygen (1, 2, 20, 21, 22). While the first four experiments indicated that increasing the amount of respired oxygen can increase the sensitivity of a tumour, at least as regards the initial response, there are good reasons for thinking that the answer obtained will depend upon the way in which the experiment is carried out and upon the particular tumour and host.

Cells have been found to retain their antigenic potency after a dose of x-rays sufficient to kill almost all the cells (23). Experiments on the cure of tumours by irradiation are highly sensitive to immune response (24); indeed, the dose required to effect cure is correlated inversely with the degree of the immune response invoked by the tumour (25). Any immune re-

sponse in a chosen tumour-host system may therefore be of the greatest importance, and careful consideration is needed in assessing experimental data if immune response is suspected.

Experiments on the oxygenation of tumours may be carried out to answer several questions:

(1) Is it possible to raise tissue oxygen tension in a tumour? If so, what are the optimum conditions?
(2) Do tumours contain some cells sufficiently anoxic for their sensitivity to be depressed, and can they be sensitized by oxygen?
(3) Can all the anoxic cells in the tumour be adequately oxygenated by a particular procedure?

Various host-tumour systems may be suitable for trying to answer particular questions. If a homotransplant (or isotransplant) is chosen because it has a particular histologic structure, it is first necessary to show that oxygen does not itself alter the level of graft immunity. The degree of immunity is of great importance. If a homotransplant is used in which it is necessary to kill only, say, 65 per cent of all the cells by irradiation to obtain a cure, the remainder being dealt with by the immune reaction, then modification of the sensitivity of, perhaps, 1 per cent of the cells which are anoxic may not have a detectable effect on the cure rate. Such a result might be misleading if taken as evidence for a negative answer to the first two questions. If, however, only 0.1 per cent of the tumour cells are killed by the immune reaction, and if 1 per cent of the cells are initially anoxic, the tumour cure rate may be enhanced by oxygen, thereby indicating a positive answer to questions 1 and 2, but leaving question 3 open. Immune response should have little effect on oxygen sensitization in this case.

H. S. Kaplan took the view that avoidance of risk of immune reaction was of overriding importance and advocated the use of spontaneous tumours on the grounds that they alone arouse no graft immunity. While accepting this, Scott said that the use of homografts permits a choice of tumours with a wider variety of histologic structures. Certain animal tumours have a structure which is likely to lead to areas of anoxia, not unlike those reported for certain human squamous-cell carcinomas by Thomlinson (17).

The degree of sensitization to single doses resulting from pressurized oxygen is dependent upon the stage of growth of the tumour; the effect is small in early tumours with a relatively good circulation, larger in more fully grown tumours with some congestion, but is again small in tumours which have grown so big that severe vascular occlusion occurs. Moreover, as emphasized by Thomlinson, the effect of oxygen can easily be modified by any impairment of the circulation resulting from application of a constraint to the tumour during irradiation. Another hazard in experiments with mice is the danger of haemorrhage in the lungs following exposure to oxygen at pressure above 2 atmospheres. Convulsions are not seen, however, in these mice. Another important factor is the depression of tissue oxygen tension by anaesthesia. While the oxygen tension may be raised by means of vasodilators, it is open to question whether this will apply to many tumours, because of venous obstruction. In one specific test of this point it was found that a mixture of 5 per cent CO_2 and 95 per cent O_2 was no better than 100 per cent O_2 in sensitizing the Ehrlich ascites tumour grown in solid form (26). Other physiological aids to increased tissue oxygen are respiratory poisons or antimetabolites or oxygen carriers better adapted to transporting oxygen at high oxygen tensions than haemoglobin.

PHYSIOLOGY OF TISSUE OXYGEN TENSION

C. J. Lambertsen discussed the physiology of the transport of oxygen to the tissues, with special reference to the brain. While the oxygen tension in arterial or

venous blood can be measured accurately, there are very real difficulties in measuring tissue oxygen tension. It is not clear that readings obtained with a platinum electrode can safely be interpreted in terms of tissue oxygen tension. Indeed, there is still no satisfactory method of measurement.

The oxygen tension in the blood varies along the length of a capillary, being normally about 100 mm. Hg at the arterial end and falling to about 40 mm. Hg at the venous end. The initial fall is rapid and the mean capillary oxygen tension is about 60 mm. Hg. Breathing oxygen at 1 atmosphere raises the arterial oxygen tension to over 600 mm. Hg (27). The venous tension, however, is increased only slightly, and the mean oxygen tension becomes about 120 mm. Hg. The actual drop in oxygen tension along the capillary is dependent upon the rate of blood flow and the haemoglobin concentration. Increasing the flow rate by means of vasodilators markedly increases the venous oxygen tension. Carbon dioxide is a highly efficient dilator for the cerebral circulation (28).

The amount of oxygen carried by the blood through tissue is considerably in excess of the amount utilized. This leads to the concept of tissue oxygen flow, which is defined as the number of milliliters of oxygen passing through 100 gm. of tissue per minute (29). For the brain, typical figures are 50 ml. of blood per minute per 100 gm. of tissue, each milliliter containing 0.2 ml. of oxygen, so that the flow is 10 ml. per 100 gm. brain per minute. Raising the pressure of oxygen respired has relatively little effect upon the tissue oxygen flow, 10 atmospheres pressure being needed to double the flow. Vasodilators, however, are relatively effective. For example, with respiration at 3.5 atmospheres pressure, the brain blood flow is doubled by the addition of about 2 per cent CO_2. The increased flow reduces the fall of oxygen tension along the length of the capillary and in this way could be effective in raising the mean oxygen tension in the brain. It is not known to what extent the relatively embryonic blood vessels of tumours are enervated and will respond to vasodilators.

An increase in temperature will tend to raise the blood flow and to increase the dissociation of oxyhaemoglobin, but will also enhance oxygen utilization. It is not clear how temperature will affect tissue oxygen tension in areas remote from capillary blood.

E. Renkin pointed out that the curability of a tumour may depend more upon the minimum than the mean oxygen tension. Further study is needed of the vascular system of various tumours and of the action of vasodilators on tumour circulation.

PROTECTION BY TEMPORARY ANOXIA IN ANIMAL EXPERIMENTS

E. A. Wright described experiments on the induction of anoxia in anaesthetized mice by means of nitrogen asphyxia for a period of three-quarters of a minute to a minute, following which the animals are revived. The radiosensitivity of the thymus gland to external 8-Mev beta irradiation falls by a factor of 2.5 during the first ten seconds of asphyxia and then reaches a constant level as the result, presumably, of the remaining oxygen being used up by the tissues. In this experiment, the effectiveness of the radiation is judged from the reduction in the weight of the thymus gland during the first two days following irradiation (30). Experiments have also been carried out on the effectiveness of temporary nitrogen asphyxia in protecting the animal against whole-body irradiation. A factor of 2.4 is achieved when four-second irradiations are received after twenty-five seconds in nitrogen.

With respect to the possibility of a clinical application, it is not clear whether complete anoxia can safely be achieved for short periods. A considerable degree of anoxia occurs during dental anaesthesia with nitrous oxide. Complete anoxia is tolerated locally in limbs for limited

periods, but the brain suffers irreversible damage if it is anoxic for more than about two minutes. Irradiations could be carried out very quickly if special powerful equipment were built. In view of the advantages of the anoxic method of protecting normal tissues, the problem of inducing anoxia safely deserves serious consideration.

THE MEASUREMENT OF LOCAL TISSUE OXYGEN TENSION

The measurement of the local oxygen tension in tissue depends almost entirely upon the platinum electrode method. For this a platinum cathode is used in conjunction with a nonpolarizable anode. When a suitable voltage is applied, molecular oxygen is reduced on the platinum surface and recorded as a current (31–34). *P. Naylor* described a method employing an open-end, highly polished platinum electrode in conjunction with a circuit giving saw-tooth voltage pulses every few seconds. This permits a continuous display of the voltage-current characteristics of the electrode upon a cathode-ray-tube screen. The method provides a sensitive indication of the state of the electrode surface and of whether it has been pushed into a capillary, and shows any change in oxygen available to the electrode, but the current is not related to tissue oxygen tension in any precise way. Preliminary data are available from electrodes inserted into patients undergoing x-ray treatment in high-pressure oxygen.

Experiments with electrodes maintained at a constant potential were reported by *D. B. Cater*. Inserted in the skin of rats, the electrode records an increased current when oxygen is given. Changes in the current are noted when adrenalin or vasopressin is injected (33). It may be significant that an electrode inserted into the edge of a tumour shows little increase in current when oxygen is given but, after a course of radiotherapy, the increase is much more marked, indicating a better oxygen supply during the later part of the treatment.

FUTURE DEVELOPMENTS

In the discussion concluding the Conference, *H. M. Patt, H. S. Kaplan, and L. H. Gray* reviewed the areas where experimental investigation is most needed. Little is known of the extent to which tumour cells are facultative anaerobes, or the level of oxygen tension at which they remain viable or grow. Many tumour cells must live for considerable periods under abnormal physiological conditions with inadequate removal of catabolites and poor supply of nutrients. Neither the radiosensitivity nor the critical oxygen concentration is known for such cells. It is not known, moreover, whether exponential survival curves for any mammalian cells extend with a similar exponent below a surviving fraction of about 10^{-5}. Yet the success or failure in the treatment of a tumour by irradiation may depend upon the inactivation of cells to surviving fractions of 10^{-10} or even lower.

In the face of these uncertainties, more experiments are needed on the effects of radiation on animal tumours, especially where the criterion of effect is cure. The choice of tumour and host presents problems which require the most careful consideration. Spontaneous tumours offer the best chance of freedom from immune response.[5] Transplantable tumours may be of value when parallel work *in vivo* and *in vitro* is contemplated or when particular histologic structures are required. It is most important that the results of radiation experiments should be correlated with the histologic structure of the tumour used.

In placing animals in position with the tumour in the x-ray beam, the greatest care is necessary to avoid any impairment of the circulation. Accidental occlusion of the blood supply can reduce the sensitivity of an otherwise well oxygenated tumour which may, in turn, be resensitized by the administration of oxygen. Such an experiment may show oxygen to be effective

[5] Prehn and Main (35) have demonstrated an immune response against a chemical carcinogen-induced tumour transplanted to a host from the same inbred line of mice.

in sensitizing the tumour, although this effect would be an artefact of the manner of holding the animal during the irradiation.

The measurement of tissue oxygen tension remains a problem of central importance. Refinements in the methods of constructing platinum electrodes, especially of the recessed or coated types, may lead to greater precision in the measurement of the mean oxygen tension over a small volume at the tip of the electrode. Oxygen tension measurements are particularly needed in relation to studies of the circulation in tumours.

Work with pressurized oxygen as a sensitizing agent remains logical but, because of the very serious practical difficulties in applying this on any scale, alternative approaches should be energetically explored. The administration of oxygen may be combined with drugs which reduce metabolism or with hypothermia to reduce oxygen consumption. The actions of the inert gases and nitrous oxide on oxygen tension require elucidation. It is quite practicable to use the method of anoxia for short periods during the irradiation of experimental tumours in mice, but whether short periods of complete anoxia can safely be prolonged in man is a question which poses major problems to the physiologist.

Whatever the results in animal experiments, the final answer can be obtained only from clinical trials. It seems that there is every reason to continue with and to extend the clinical tests with pressurized oxygen already in progress. The value of the work will be greatly enhanced if the groups of patients treated in oxygen are matched with control groups undergoing conventional treatment. Only by so doing can it be discovered whether tissue oxygen tension can be advantageously manipulated in such a way as to increase the proportion of patients cured by radiotherapy.

SUMMARY

A review and bibliography on tissue oxygen tension and radiotherapy are given, based on a conference held in Burlington, Vermont, in August 1958. The subjects covered include the oxygen effect in radiobiology, tumour morphology and circulation in relation to oxygen tension, problems in design of radiation experiments on animal tumours, physiological factors in tissue oxygen tension and its measurement with the aid of platinum electrodes, protection by temporary anoxia in animal experiments, and x-ray therapy in oxygen. The field is reviewed and areas where further work may be profitable are discussed.

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SUMMARIO IN INTERLINGUA

Tension Oxygenic de Tissu e Radiotherapia. Un Revista e Bibliographia Basate Super le Conferentia a Burlington, Vermont, in Augusto 1958

Es presentate un revista e bibliographia de tension oxygenic de tissu e radiotherapia, basate super un conferentia tenite a Burlington, Vermont, in augusto 1958. Le themas includite es effecto de oxygeno in radiobiologia, morphologia e circulation tumoral in relation al tension oxygenic, problemas in le planation de experimentos con radiation de tumores animal, factores physiologic in tension oxygenic de tissu e le mesuration de illo per medio de electrodos de platino, protection per anoxia temporari in experimentos animal, e therapia a radios X in oxygeno. Le campo es revistate, e areas es discutite in que labores additional esserea profitabile.

Meckel's Diverticula: Preoperative Roentgen Diagnosis in Children

Presentation of Two Cases[1]

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IN SPITE of the finding of Meckel's diverticulum in 1 to 2 per cent of all necropsies (1, 2), its preoperative roentgen diagnosis constitutes a rarity. Stein *et al.* (2), in a review of the English literature found only 33 instances in which the diagnosis of Meckel's diverticulum had been made preoperatively. They report 5 additional cases in adults, bringing the total to 38 at the time of their publication.

Two cases of Meckel's diverticulum in children with preoperative roentgen diagnosis will be reported here. These were consecutive cases studied with this possibility in mind in an interval of three weeks. The presenting complaint in each was periumbilical abdominal pain. This symptomatology and absence of demonstrable disease in the upper gastrointestinal tract prompted distal small bowel study in an attempt to demonstrate a Meckel's diverticulum.

REPORT OF CASES

CASE I: D. C., a 6-year-old white boy, was first seen on May 11, 1959, complaining of intermittent dull aching periumbilical pain during the past year. He frequently had to stop even play activity and lie down until the pain disappeared. During the past three weeks the pain had become more frequent and severe, occurring both day and night. He had vomited on only one occasion, the night prior to the initial visit.

The patient was placed on medication and seen four days later, at which time his complaint was the same except that the abdominal pain had become more or less constant. At this time physical examination revealed mild tenderness in the periumbilical area but was otherwise normal. Urinalysis was normal. The white blood count was 7,300, with 27 per cent neutrophils, 50 per cent lymphocytes, 5 per cent monocytes, and 10 per cent eosinophils.

Roentgen study was done on May 18. Since the esophagus, stomach, and duodenum appeared normal, it was decided to observe the distal small bowel in an attempt to demonstrate a Meckel's diverticulum. Fluoroscopy was done after an interval of one hour, at which time the barium had advanced to the cecum. At once a diverticulum-like structure was identified, originating from the prepelvic portion of the ileum and directed laterally across the terminal ileum approximately 5 cm. proximal to the ileocecal junction. This appeared as a pouch 2 cm. in diameter, somewhat lobulated in configuration and constricted at the neck at the point of junction with the prepelvic section of the ileum (Fig. 1). On this evidence a roentgenologic diagnosis of Meckel's diverticulum was made.

Fig. 1. Case I.

Surgery was undertaken one week after the roentgen demonstration of the diverticulum. At lap-

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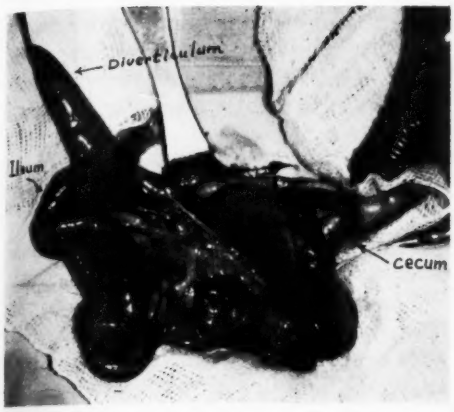

Fig. 2. Case I. Surgical specimen

arotomy, through a right lower quadrant incision, a Meckel's diverticulum was found approximately 35 cm. proximal to the ileocecal valve, measuring approximately 7 cm. in length and 1 cm. in diameter (Fig. 2). A band-like structure tended to draw the diverticulum toward the cecum and probably accounts for the position as observed at fluoroscopy and demonstrated on the spot-film. Numerous large mesenteric nodes were present. The Meckel's diverticulum was excised, and the postoperative course was uneventful.

The pathological report was Meckel's diverticulum and subacute Meckel's diverticulitis. No aberrant tissue was noted.

CASE II: C. G., an 8-year-old white boy, was first seen in this Clinic on June 3, 1959, with a history of recurrent, moderately severe periumbilical cramping pain associated with daily vomiting for a week and a half. There had been slight elevation of temperature, some days to 100°, orally. No other complaint referable to the gastrointestinal tract was elicited. Physical examination revealed a mild degree of pectus carinatum. Mild tenderness was present throughout the abdomen, but without muscle spasm or rebound tenderness. No other abnormalities were found on physical examination. Urinalysis was normal. The white blood count was 6,100, with a normal differential count.

Roentgen examination was done on June 5. The esophagus, stomach, and duodenum appeared normal and the possibility of a Meckel's diverticulum was considered. At fluoroscopy, at the one-hour interval, the barium had advanced to the cecum. At this time, deep in the pelvis a small bud-like structure, 8 mm. in diameter, was observed and found to be an outpouching from a diverticulum measuring approximately 2.5 cm. in diameter. There was localized constriction at the neck of the bud-like outpouching at the point of junction with the main diverticulum, as well as narrowing of the neck of the

Fig. 3. Case II.

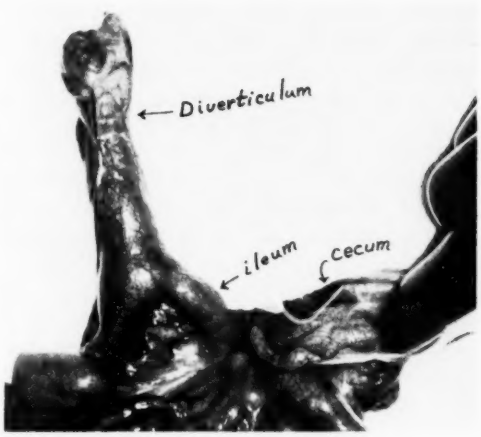

Fig. 4. Case II. Surgical specimen

latter at the point where it joined the ileum. The diverticulum presented a somewhat lobulated appearance (Fig. 3). A roentgenologic diagnosis of Meckel's diverticulum was made.

At laparotomy, one week later, through an incision in the right lower quadrant, approximately 35 cm. proximal to the ileocecal valve, there was found a Meckel's diverticulum measuring approximately 12 cm. in length and 1.5 cm. in diameter (Fig. 4). There was marked mesenteric lymphadenopathy. The diverticulum was excised, and the postoperative course was uneventful.

The pathological report was Meckel's diverticulum with a small secondary diverticulum at the fundus and a small nodule of pancreatic tissue in the main portion of the diverticulum. No other aberrant tissue was noted.

DISCUSSION

There are two points of interest in these case reports. The first is the preoperative roentgen demonstration of two cases of Meckel's diverticulum in children in a short interval of time, with the diagnosis made in advance of surgery and confirmed at operation. While the search for these lesions was motivated by the symptomatology and the normal appearance of the upper gastrointestinal tract, the surgical finding of mesenteric adenopathy in each instance suggests that the symptoms may actually have resulted from mesenteric adenitis and that the discovery of a Meckel's diverticulum was fortuitous.

The second point of interest lies in a comparison of the roentgen appearance of the diverticula with the gross appearance. Both were seen as pouch-like structures with a rather narrow neck at the point of junction with the ileum, resembling roentgenographically duodenal diverticula. Anatomically, however, they were demonstrated to be broad finger-like projections with no point of narrowing at the junction with the ileum, the lumen being of the same diameter throughout.

On a review of the literature it is noted that in some of the cases the roentgenographic picture has corresponded to the anatomical appearance, whereas others presented as pouch-like structures. Of similar interest is the fact that the small pouch-like projection in the second case also showed a narrow neck at the point where it arose from the main diverticulum, though anatomically no such harrowing was present.

It is believed that these two cases illustrate the value of a search for Meckel's diverticulum when the clinical picture suggests this possibility. In view of the fact that these structures are confined to the lower ileum (stated to occur within 100 cm. of the ileocecal junction in all instances though in a case reported by Stein *et al.*, in an adult, the distance was 150 cm.), it is believed that proper timing of the fluoroscopic examination may result in higher yield of preoperative diagnoses and yet keep to a minimum the amount of exposure to which the patient is subjected. In each of the cases presented, the fluoroscopy was done one hour after administration of the barium mixture, at which time it was possible to evaluate the distal ileum to the cecum. By judicious use of a small field at fluoroscopy and confining the examination to the time when the barium should have arrived in the lower ileum, the exposure is limited and yet adequate study of the ileum can be achieved. It is believed that without fluoroscopy and spot-filming a considerably lower percentage of these structures would be demonstrated roentgenologically.

SUMMARY

Two cases of Meckel's diverticulum in children seen within a period of three weeks, diagnosed roentgenologically and proved surgically, are reported. These are believed to bring the total number of cases of Meckel's diverticulum in the English literature with a preoperative diagnosis to 40.

In view of the symptoms in these cases, notably periumbilical pain, and the absence of demonstrable disease in the upper gastrointestinal tract, examination was specifically directed to the possible presence of a Meckel's diverticulum.

A comparison of the roentgen picture and the anatomical appearance showed one notable difference. While the diverticulum was seen roentgenologically as a pouch-like structure, with a narrow neck at the point of junction with the ileum, no such narrowing was present in the operative specimen.

The surgical demonstration, in each case, of rather marked mesenteric adenopathy suggests that this may have been the source of the symptomatology and that the discovery of the diverticulum was purely fortuitous.

Fluoroscopy and spot-filming are considered of importance in the demonstration of a Meckel's diverticulum. With a small field and proper timing of the fluoroscopic examination radiation exposure of the patient is minimized.

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SUMMARIO IN INTERLINGUA

Diverticulos de Meckel: Pre-Operative Roentgeno-Diagnose in Juveniles. Presentation de Duo Casos

Es reportate duo casos de diverticulo de Meckel in patientes pediatric, vidite intra un periodo de tres septimanas e diagnosticate roentgenologicamente, con verification al operation. Assi, nos crede, le numero total de diverticulo de Meckel con diagnose pre-operatori reportate in le litteratura de lingua anglese monta a 40.

In vista del symptomas in le presente casos—specialmente dolores periumbilical —e le absentia de un demonstrabile morbo in le vias gastrointestinal superior, le examine esseva concentrate specificamente super le possibile presentia de diverticulo de Meckel.

Un comparation del imagine roentgenoscopic con le apparentia anatomic monstrava nulle notabile differentia. Durante que le diverticulo se presentava in le roentgenogramma como un structura bursiforme con un collo restringite al puncto de su junction con le ileum, nulle tal restriction esseva presente in le specimen chirurgic.

Le demonstration chirurgic, in ambe iste casos, de satis marcate grados de adenopathia mesenteric suggere que isto esseva possibilemente le base del symptomatologia e que le discoperta del diverticulo esseva purmente fortuite.

Fluoroscopia e roentgenogrammas centrate es considerate como importante in le demonstration de diverticulos de Meckel. Con le uso de un micre campo e del correcte chronometria in le examine fluoroscopic, le radio-exposition del patiente es reducite al minimo.

A Simple Method for the Mensuration of Body Contour[1]

PAUL W. SCANLON, M.D.

ACCURATE measurement of body contour and the transposition of this contour to the plotting board are integral but tedious parts of all but the most simplified forms of planning for radiation therapy. The use of a rotation therapy unit and a light-beam triangulation device ordinarily employed to measure source-to-skin distances has been found to provide an easy and convenient substitute of comparable accuracy for the more time-consuming conventional methods.

The usual technics for the mensuration of body contour, such as those which employ the bending of malleable wire or solder about the part, the use of plaster-cast contours, the spoke-and-wheel device which employs movable radii of measured length, and even the more elaborate projection methods in which cross-sectional contours of the body are projected against a patient's dimensions on the plotting board, are too well known to warrant elaboration here. All are time-consuming procedures which have inherent inaccuracies, probably the most important of which is due to the need for transposing onto the plotting board the location of the tumor to simulate actual conditions of treatment.

A system which employs the actual location of the tumor as a fixed point of reference for the measurement of varying tumor-skin radii bypasses some of the inaccuracies of the conventional methods. The body contour and its relationship to the underlying mass are mapped directly on the patient, the only prerequisites being a rotational therapy device capable of 360° rotation and a light-beam source-to-skin measuring device such as that shown in the accompanying figure.

This light-beam device is capable of measuring source-to-skin distances of 40 to 60 cm. by adjustment of the light-beam

Fig. 1. Source-to-skin light-beam measuring device currently used on the rotational unit described in the text.

spot to the cross-hair shadow of the field lights, the source-to-skin distance being read directly from the scale on the device. The skin-tumor radius of any desired vector is obtained directly by the simple expedient of positioning the tumor at the axis of rotation. With our unit, which employs a rotational radius of 55 cm., the source-to-skin distance is determined with the light beam and this value is subtracted from 55 cm., the difference representing the skin-tumor radius of the particular vector. The same process is repeated every 30° around the circumference of the part, and within a short time an accurate cross-sectional contour is obtained.

Accurate localization of the area to be treated is, of course, essential, but since this is a necessary step preliminary to any technic of body-contour plotting, it need not enter into special consideration with the particular method under description. Once the necessary markings are placed on the skin, conforming to the anteroposterior and lateral co-ordinates of the tumor area, obtained either by localizing roentgenograms or fluoroscopy, the patient is placed exactly as for rotational therapy. The

[1] From the Section of Therapeutic Radiology, Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

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field light and back-pointer light are used to align the lateral co-ordinates, and a pin-and-arc device, with the bar set at the correct rotational radius and the pin set to the correct tumor depth, is employed, so that positioning of the tumor at the axis of rotation is readily achieved with a minimum of difficulty. Once this is done, the machine head is swung manually around the circumference of the patient so that source-to-skin distances are obtained at every 30° vector or whatever angle is desired. The differences between these varying source-to-skin distances and the rotational radius of 55 cm. of course represent the actual skin-tumor radii.

When rotational therapy is used, tumor-air ratios are obtained directly from tables without the need for plotting the body contour and the corresponding tumor location, provided that no more than axis-dose measurements are required. When off-axis points are to be measured and a more elaborate isodose plotting is required, it is relatively easy with a ruler and protractor to draw out the varying skin-tumor radii, connect their ends, and obtain an accurate cross-sectional contour which can then be plotted in the conventional manner.

Comparison of the above method of contour plotting with the more conventional methods has satisfied the writer that it possesses a comparable degree of accuracy. The method is easy, timesaving, and convenient, since in most cases the measurements required can be carried out in the treatment room. There are, however, a few minor inconveniences which should be mentioned. As the source head swings under the table, the scale on the light-beam measuring device becomes inverted and, in this low, upside-down position, accurate reading of the scale requires a degree of physical dexterity.

Our rotational treatment couch has a curved sliding top which closely approximates the posterior aspect of the torso. Hence, all measurements of the torso can be made with a single placing of the patient in the supine position, incorporating the table top in the data or diagram as it should be. When, however, an ordinary flat treatment couch is used, or when the head and neck are to be measured and the curving table top does not conform to their posterior contours, it becomes necessary first to measure the anterior half of the part with the patient in the supine position, and then to reposition him face down in the prone position and measure the posterior half in exactly the same manner.

The light-beam device which we currently use[2] is calibrated for source-to-skin distances of 40 to 60 cm. This means that when a rotational radius of 55 cm. is used, skin-tumor distances of more than 15 cm. cannot be measured directly by adjusting the light-beam spot to the cross-hair shadows of the field light. When such long skin-tumor distances are encountered, as they usually are around the wide aspects of the pelvis and shoulders, an accurate approximation can be made in the following manner:

With the light-beam scale set at the extreme limit of its excursion (40 cm.), which would correspond to a skin-tumor radius of 15 cm., the distance on the patient's skin from the light-beam spot to the cross-hair shadow of the field light is measured. This distance (in centimeters) is added to 15, and the sum obtained is accurate to within 0.25 to 0.50 cm. of the actual skin-tumor radius of that particular vector. Although this additional correction is easy to make, it is hoped that in the future the scales on light-beam source-skin measuring devices can be extended from 60 to 35 cm., thus permitting easy measuring of all skin-tumor radii up to 20 cm., the probable extreme range which might be encountered in clinical rotation therapy.

SUMMARY

A relatively easy method of obtaining an accurate cross-sectional body contour by use of a rotational therapy unit and a light-beam device ordinarily employed for the measurement of source-to-skin distances is described.

[2] Standard equipment on the Picker C-1000 unit.

SUMMARIO IN INTERLINGUA

Un Simple Methodo pro le Mensuration del Contornos del Corpore

Le obtention de accurate mesuras del contorno corporee es un parte integral del planation radiotherapeutic. In le technicas usual, le transposition del contorno a un planca topometric (in que le sito del tumor es indicate) resulta facilemente in inaccuratias. Iste difficultate es evitate in le hic describite methodo que utilisa le ver sito del tumor como puncto fixe de referentias in le mesuration de varie radios inter tumor e pelle.

Le contorno del corpore e su relation al area de tractamento es mappate directemente sur le patiente con le adjuta de un apparato de therapia rotational e un dispositivo a fasce de lumine pro le mesuration del distantias fonte a pelle. Le radio de pelle a tumor o non importa qual altere vector desirate es obtenite directemente per le simple processo de positionar le tumor in le axe de rotation. In le caso del apparatura usate per le autor, le radio rotational es 55 cm. Ab iste cifra, le distantia inter fonte e pelle (determinate per le fasce de lumine) es subtrahite. Le resultato representa le radio de pelle a tumor. Per repeter le procedimento a appropriate intervallos circum le circumferentia del parte in question, un accurate contorno de section transverse es obtenite.

The Inherent Filtration of X-Ray Tubes[1]

K. REINSMA

As MANY recommendations on radiation protection mention the total filtration demanded in diagnostic radiology, there is a growing interest in a relatively simple method for evaluating the inherent filtration of the x-ray tube. With this knowledge, it is possible to add extra filters to arrive at the prescribed total filtration.

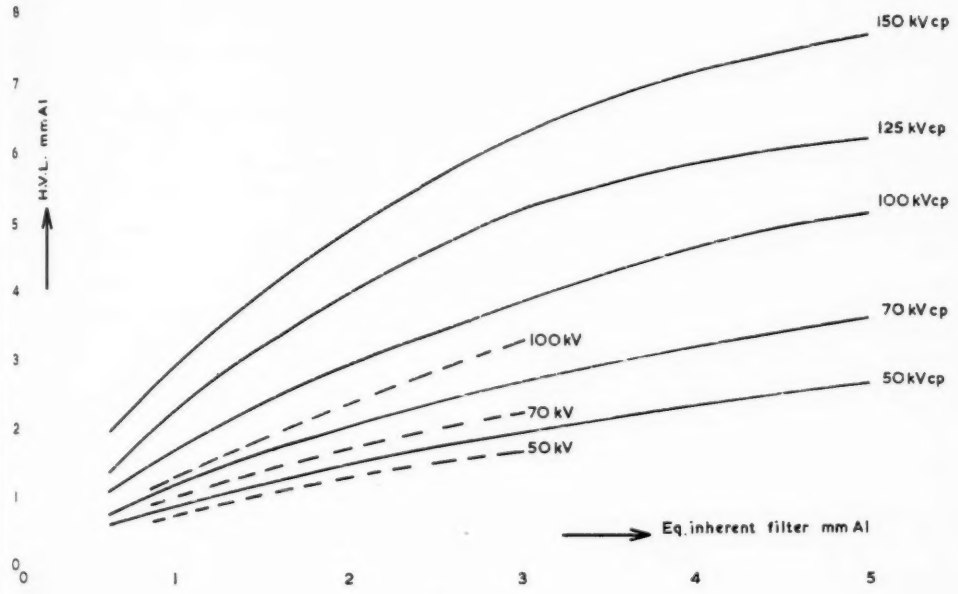

Figure 1

When considering the inherent filtration equivalent of x-ray tubes, one must bear in mind the fact that this inherent filtration depends on the tube voltage and the wave form. Further, one can think of the inherent filtration equivalent with respect to the absorption of the x-rays (1) or with respect to their resulting quality, characterized by the half-value layer expressed in terms of the equivalent filter material.

Trout and his associates (2) published a simple experimental method for determining the inherent filtration of diagnostic x-ray tubes. A satisfactory value, they stated, can be obtained by determining the half-value layer of the unfiltered beam and relating this to the thickness of aluminum, for instance, which must be added to a beryllium-window tube to produce the same half-value layer under similar conditions. These workers published a number of curves with the half-value layer plotted against inherent filtration aluminum equivalent, with the tube voltage (kvp) as a parameter. No mention was made, however, of the wave form. Actually, according to a personal communication from Mr. Trout, the wave form used was "full-wave" rectified and as close to a sine-wave as one ever sees on diagnostic equipment. We made some similar measurements, for which we used a

[1] From Philips' Phys. Techn. X-Ray Laboratory, Eindhoven, The Netherlands. Accepted for publication in June 1959.

TABLE I: QUALITY OF THE RADIATION EMITTED BY A DIAGNOSTIC X-RAY TUBE (WITHOUT EXTRA FILTER)

Tube Potential (kvp)	—Half-Value Layer in mm. Al— Constant Potential	Full-Wave Rectified
50	1.25	1.16
100	2.75	1.9
125	3.2	2.3

constant potential wave form. Our curves are shown in Figure 1, along with the curves published by Trout *et al.* (broken lines) for corresponding tube voltages and full-wave rectified wave form.

TABLE II: INHERENT FILTRATION EQUIVALENT OF A DIAGNOSTIC X-RAY TUBE

kvcp	—Equivalent Inherent Filtration— From Measurements of Reduction in Exposure Dose	From h.v.l. Measurements
50	1.7	1.4
100	1.9	1.8
150	2.1	1.8

To check the above method we measured the quality of the radiation from a diagnostic x-ray tube for two wave forms, *viz.* constant potential and full-wave rectified. The results are given in Table I. With the aid of a cut-away tube unit we also measured the inherent filtration equivalent with respect to the absorbing properties as a function of the tube voltage for constant potential. These results are given in Table II.

CONCLUSIONS

1. For a given voltage the radiation quality of an x-ray beam, expressed in mm. Al h.v.l., depends strongly on the wave form.

2. There is relatively a great difference in inherent filtration equivalent depending on whether one considers this with respect to adsorption of the x-rays or to radiation quality.

3. For the determination of the inherent filtration equivalent with respect to the radiation quality, one can make use of the set of curves as shown in Figure 1.

Philips' Phys. Techn. X-Ray Laboratory
Eindhoven, The Netherlands

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SUMMARIO IN INTERLINGUA

Filtration Inherente in Tubos de Radios X

Si le filtration inherente in un tubo de radios X es cognoscite, il es possibile determinar le quantitate de filtration additional requirite pro obtener le prescribite total.

Pro un voltage particular, le qualitate del fasce de radios X, experimite in mm. devalor de medie spissitate in Al, depende fortemente del forma del unda (potential constante o rectification de unda integre). Il existe un relativemente marcate differentia in le equivalente del filtration inherente secundo que isto es considerate con respecto al absorption del radios X o al qualitate del radiation.

Es reproducite un serie de curvas con le adjuta del quales le equivalente de filtration inherente pote esser determinate con respecto al qualitate del radiation. Insimul con le curvas del autor, obtenite con un forma de unda a potential constante, curvas es presentate que esseva publicate per Trout e su collaboratores pro rectification de unda integre.

EDITORIAL

Radiologists and Epidemiology

A new chapter in the medical detective story about neoplastic disease following irradiation in childhood is presented by Doctors Saenger, Silverman, Sterling, and Turner in this issue of RADIOLOGY. It is an important contribution to our knowledge of radiation effects, made through skillful use of the research methods of epidemiology.

Some of the findings might have been predicted from previous work: the greatly increased incidence of thyroid cancer in the irradiated children, for example. On the other hand, the increased leukemia incidence which some investigators have observed after irradiation was not found. The irradiated children had a distinctly higher percentage of disabling diseases in general than their siblings but, most surprisingly, a substantially lower total mortality than either siblings or the general population. This is a highly provocative study, and the thoughtful, scholarly, and sophisticated discussion given by the authors is as valuable as are the data they present. The problems remaining unsolved at the end of the study are fairly stated; at the same time, some practical conclusions are suggested for radiologists who must continue to treat sick children without waiting for all of these problems to be solved.

Epidemiological studies like this one are becoming more and more important in medical research. The epidemiological method uses statistical technics to make comparisons between large groups of individuals. Properly applied, it can uncover important facts about the nature and causes of disease that might not come to light in any other way. It represents virtually the only means of studying the subtle effects upon human health of such environmental agents as ionizing radiation, tobacco smoke, petroleum fumes, etc. Such investigations might even lead to discovery of the principal causes of cancer. Unfortunately, studies of this type are not easy, either to conduct or to interpret. The investigator and the critical reader must constantly be on guard against at least three major sources of possible error.

First, there is the problem of determining what the study group really represents. It is obvious that finding a difference between two groups of persons will have little usefulness in medicine unless it leads to conclusions that apply to other persons. It is not so obvious, but has been demonstrated by many unfortunate experiences, that groups which happen to be easy to study are often not representative of the population from which they are taken and, furthermore, that two populations are often not directly comparable. An example of populations which do not lend themselves to direct comparison is seen in the recent study showing the mean age at death for radiologists to be five years less than for other physicians. Many physicians who did not have epidemiological training interpreted this to mean that radiologists have a shortened life-expectancy. Later, it was demonstrated that these two populations had quite different age-distributions, which alone could fully account for the difference observed in mean age at death (10). There are good modern epidemiological methods of sampling and of testing the comparability of populations which can do much to reduce these errors, but their use requires knowledge and often considerable labor. Dorn (3) states: "The fundamental defect of many retrospective studies is that they are based on an un-

specified sample of persons chosen by an unknown method of sampling from an unidentified population."

Second, the investigator must try to calculate the odds that his findings may be due to chance alone. Many good tests have been devised for this. They are all based upon mathematical models. In general, they require that the individual values comprising the data follow some specific distribution form, such as the well known normal curve. If the data depart too widely from the distribution for which the test is designed, the mathematical conclusion may be invalid and overestimate the significance of a difference between groups (9). Unfortunately, the test itself has no sense of responsibility at all; once it has been applied to the data it unfalteringly delivers a numerical probability value, no matter how erroneous it may be. Lombard (8) cites a statement made by Hoffman in the early part of this century: "Statistics are chiefly an auxiliary method in connection with scientific enquiries; but it is none the less necessary to caution the inexperienced against the use of a method or science which on its own account requires as much study and consideration, and as much practical experience, as medicine or surgery or both combined."

It must further be remembered that, whatever numerical probability criterion one accepts as evidence that a correlation between two groups is too great to attribute to chance, one can expect to be wrong with that same numerical frequency. Thus, if twenty seasoned investigators go fishing in the same pool, it stands to reason that one of them will get a remarkable number of fish, a number having only a 5 per cent probability of being due to chance. It is the lucky angler who will do all the bragging; the others may not even mention that they went fishing. Sterling (11) has pointed out a similar situation in modern scientific communication: research results which are statistically "nonsignificant" may tend to be left unpublished and other investigators may unknowingly repeat the studies independently until eventually by chance a "significant" result occurs—and that is the only one which is published. Thus, the archives may become loaded with experimental results which are in fact oddities of chance. If one tries to avoid this type of error by accepting only very high probability values, then correlations which are meaningful and perhaps highly important may be rejected, since the amount of data required to show very high probability values is often more than is practical to obtain.

Third is the matter of cause and effect. On our street, the morning paper arrives shortly after the milk, with a high degree of statistical association, but no one thinks that one causes the other. Statistical information may be the key to discovery of cause and effect relationships, but supplementary evidence must be advanced to support the hypothesis that one event is capable of causing another before such a relationship can be accepted (5).

To make things still more difficult, the causation of an event commonly depends upon multiple factors acting together. The paper is delivered if it is morning *and* if the paperboy has been paid; neither condition alone is sufficient. Studies of one variable which fail to control the other(s) may thus give conflicting results. The inconsistency of present data on the occurrence of leukemia after irradiation (6) could arise from such a compound relationship.

Listing these three pitfalls is intended to show that epidemiology is not an easy science. It seems a pity to ask hard-working radiologists to add it to the burden of knowledge already expected of them. But, if this powerful research method is to be used productively in attacking radiological problems, radiologists will have to learn at least enough of the rudiments of the discipline to enable them to communicate satisfactorily with professional epidemiologists when formulating investigations, and they will also need this knowledge to evaluate properly the studies conducted by their colleagues.

Radiologists, like other clinicians, often find the technical literature of epidemiology and statistics difficult to understand because it is so formidably couched in mathematical symbols and esoteric terminology. It may be of service to list a few of the excellent recent reviews which do not present this obstacle (1–3, 5–8). We know of no recent statement, however, more timely than one made by Frost (4) in 1925: "It is frequently easy to exhibit some figures which, though not really to the point, will nevertheless serve to impress an uncritical public, and the temptation may be great to give them, at least by implication, an unduly favorable interpretation. It is more difficult and more tedious to present the full argument, based on all the facts, and it is perhaps a little humiliating to admit that the statistical evidence is deficient because we have failed to collect it; but to do this is not only more scientific, it is in the end more convincing, and after all there is no free choice, because it is the only *honest* method, whether it be convenient or not. Finally, it is the only way of progress, for the first step towards collecting better evidence is to recognize the deficiencies of that which is at hand."

The further investigation of somatic and genetic effects of small doses of ionizing radiation in man is an urgent need which requires the most rigorous application of sound epidemiological principles. We are already being forced to make decisions with regard to the potential hazards of radiation despite many deficiencies of present information about these hazards. Work of the caliber of that reported by Saenger and associates is essential for the continual reappraisal of our concepts of radiation dangers. "To unravel the tangled skein of causation of disease by the observation of man in his environment," says Dorn, "requires the utmost persistence, a profound skepticism of the obvious, an alertness for the selective factors that have produced the most readily available subjects for study, the ability to penetrate beneath the surface of the observations, a strong distrust of what is said or seen, since the unchecked human memory is probably the most unreliable research instrument in existence, and a willingness to spend long hours upon the development and perfection of methods of making observations coupled with the patience to await the occurrence of the succession of events most relevant to the hypotheses to be tested."

ANTOLIN RAVENTOS, M.D.

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ANNOUNCEMENTS AND BOOK REVIEWS

CHICAGO ROENTGEN SOCIETY

Newly elected officers of the Chicago Roentgen Society are: President, George B. Cahill, M.D., Flossmoor; Vice-President, Robert M. Potter, M.D., Chicago; Secretary-Treasurer, William F. Hutson, M.D., 5145 North California Ave., Chicago 25, Ill.

Meetings are held at the Sheraton Hotel the second Thursday in October, November, January, February, March, and April at 8:00 P.M.

NEW YORK ROENTGEN SOCIETY

The new President of the New York Roentgen Society is Frank J. Borrelli, M.D. Other officers are: William B. Seaman, M.D., Vice-President; Albert A. Dunn, M.D., 428 W. 59th St., New York 19, N. Y., Secretary; Bernard Wolf, M.D., Treasurer; Ramsay Spillman, M.D., Historian; Harold G. Jacobson, M.D., Member of Executive Committee.

SOUTHWESTERN RADIOLOGICAL SOCIETY

The Southwestern Radiological Society has recently elected to office: Ezra K. Neibich, M.D., Las Cruces, N. Mex., President; Ralph S. Clayton, M.D., 1501 Arizona, Building 2-A, El Paso, Texas, Secretary-Treasurer.

Meetings are held the last Friday of each month at 6:30 P.M. in the Paso Del Norte Hotel, El Paso.

TENNESSEE RADIOLOGICAL SOCIETY

The new officers of the Tennessee Radiological Society are as follows: President, George K. Henshall, M.D., Chattanooga; President-Elect, Edward H. Mabry, M.D., Memphis; Vice-President, M. D. Ingram, Jr., M.D., Nashville; Secretary-Treasurer, James J. Range, M.D., P. O. Box 324, Johnson City. Councilors nominated for the American College of Radiology are Walter D. Hankins, M.D., Johnson City, and Alternate, J. Marsh Frère, M.D., Chattanooga.

POST GRADUATE COURSE IN OCULAR RADIOLOGY

The Institute of Ophthalmology of the Americas announces a Post Graduate Course in Ocular Radiology, including both diagnosis and radiation therapy, to be offered Nov. 7–10, 1960. Details regarding registration and fees may be obtained from Mrs. Tamar Weber, Registrar, Institute of Ophthalmology of the Americas, New York Eye and Ear Infirmary, 218 Second Ave., New York 3, N. Y.

Books Received

Books received are acknowledged under this heading, and such notice may be regarded as recognition of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

MEDICAL PHYSICS. VOLUME III. Edited by OTTO GLASSER, Ph.D., Diplomate in Radiological Physics, American Board of Radiology; Professor of Biophysics, Frank E. Bunts Educational Institute; Head, Department of Biophysics, Cleveland Clinic Foundation; Member, Council on Medical Physics, American Medical Association. A volume of 754 pages, with numerous figures and tables. Published by The Year Book Publishers, Inc., Chicago, Ill., 1960. Price $25.00.

BREAST CANCER: FACTORS MODIFYING PROGNOSIS. By A. J. DELARIO, M.D., Member of the International College of Radiology, the American College of Radiology, the American Board of Radiology, the Radiological Society of North America, the Radiological Society of New Jersey, and the Scientific Advisory Council of the New York Cancer Research Institute, New York, N. Y.; Consultant Radiologist, St. Joseph Hospital, Paterson, N. J. A volume of 208 pages, with 137 tables. Published by The Macmillan Company, New York 11, N. Y., 1959. Price $7.50.

ESTROGEN-INDUCED TUMORS OF THE KIDNEY IN THE SYRIAN HAMSTER. By HADLEY KIRKMAN. National Cancer Institute Monograph No. 1. A monograph of 140 pages, with 34 plates. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1959. Price $1.25.

CONTRIBUTION À L'ÉTUDE DU SYNDROME MÉDULLAIRE APRÈS IRRADIATION: ÉTUDE EXPÉRIMENTALE. By HENRI MAISIN, Agrégé de l'Enseignement supérieur, Docteur en électroradiologie. A volume of 378 pages, with 80 figures. Published by Arscia S. A., 60, rue de l'Étuve, Brussels, Belgium, 1959. [With a Discussion and General Conclusions in English.]

Book Reviews

X-RAY TECHNOLOGY. By CHARLES A. JACOBI, B.Sc., R.T.(A.R.X.T.), M.T.(A.S.C.P.), Chairman, Medical X-Ray Technology, Oregon Technical Institute, Oretech Branch, Klamath Falls, Ore.; Chairman, Education Committee, Oregon

Society of X-Ray Technicians; Chairman, Education Committee, Northwest Conference of X-Ray Technicians; formerly Chief X-Ray and Medical Technologist, Medical Services Division, Atomic Energy Commission, National Reactor Testing Station, Idaho Falls, Idaho, AND DONALD E. HAGEN, R.T.(A.R.X.T.), Technical Supervisor for C. Todd Jessell, M.D., and George R. Satterwhite, M.D., Radiologists, Portland, Ore.; formerly Instructor, Medical X-Ray Technology, Oregon Technical Institute, Oretech Branch, Klamath Falls, Ore. A volume of 454 pages, with 220 illustrations, Published by The C. V. Mosby Co., St. Louis, Mo., 2d ed., 1960. Price $10.00.

This book, by two x-ray technicians, is designed to cover the fundamentals of x-ray technology as well as its applications. Unfortunately its language is confusing and inaccurate and the sentence structure in some cases is difficult to follow. Of the 320 illustrations a high percentage are taken from other sources in the literature. Particularly is this true of the illustrations of positions, the majority of which are from a book that is far superior in its presentation of the material.

The best thing about this work is the Appendix, which contains a table of the elements, some "useful constants, laws, definitions, and formulas," a list of electrical symbols, a table comparing tungsten with some other elements as a target, and a generous glossary of terms used in roentgenography. Otherwise the authors have little to offer.

RÖNTGENDIAGNOSTIK DES MAGEN-DARMKANALS. By Prof. Dr. R. PRÉVÔT, Hamburg, AND Priv.-Doz. Dr. M. A. LASSRICH, Hamburg. A volume of 346 pages, with 544 figures. Published by Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1959. Distributed in the United States and Canada by Intercontinental Medical Book Corporation, New York 16, N. Y. Price DM 119.—($18.50).

This book is devoted to the radiographic description and differential diagnosis of the entire gastrointestinal tract. The body of the work is by Professor Prévôt, while the pediatric aspects have been covered by Dr. Lassrich.

After a general introduction and discussion of contrast media, the use of scout films, and the basic application of mucosal studies and spot-film technics, forty-five pages are devoted to the esophagus. The next chapter, of sixty-three pages, has to do with the stomach and includes interesting roentgenograms, particularly of cases which were followed from the early stages of gastritis to obvious carcinomatous change. The emphasis on this subject is clearly due to the influence of the school of Konjetzny, to whom this book is dedicated. In the next chapter, of nineteen pages, the duodenum is discussed, and in the following fourteen pages the findings in the postoperative stomach and gastroenterostomies are explained. Forty-nine pages are given over to the small intestine and fifty-nine to the large bowel, including twenty pages on intestinal tuberculosis. The text concludes with chapters on the gallbladder and biliary tract, the pancreas, and acute abdominal diseases in the newborn and adults. A bibliography of 23 pages is appended.

This book contains excellent reproductions and affords interesting reading, but in some parts seems rather sketchy and unbalanced. For example, only four pages are devoted to diseases of the pancreas, and the important diagnostic signs of early pancreatic neoplasms are not even mentioned, except for the classical description of the known Frostberg sign and very obvious pressure defects in the duodenal loop. In contrast, nearly twenty pages are assigned to tuberculosis of the small and large intestine. While this disease may be more common in Germany than in the United States, certainly pancreatic neoplasms are probably seen as often in Europe as they are here.

The book should be of some interest to radiologists and gastroenterologists, though one cannot but feel that it is, at least to some extent, outdated.

RÖNTGENANATOMIE FÜR ÄRZTLICHES HILFSPERSONAL UND RÖNTGENTECHNIKER. By Dr. med. WOLFGANG FRIK, Privatdozent der med. Strahlenkunde, med. Klinik mit Poliklinik der Universität Erlangen, AND ULRICH GOERING, Ingenieur der Entwicklungsabteilung der Siemens-Reiniger-Werke A.G., Erlangen. A monograph of 84 pages, with 71 figures. Published by Georg Thieme, Herdweg 63, (14a) Stuttgart, Germany, 1959. Distributed in the United States and Canada by the Intercontinental Medical Book Corporation, New York 16, N. Y. Price DM 12.—($2.85).

The high-school graduate who is fortunate enough to obtain a position as a technical aid in the field of medicine will find in this rather elegant booklet brief and very elementary reference work on basic anatomy. It is leveled at about the twelfth grade. It presupposes no prior medical or roentgen experience, nor indeed any scholarship in the field of roentgenology. Under various influences and conditions, hospitals, radiologists, general practitioners, and others who own roentgen machines are apt to acquire totally untrained help. This little book is for such employees.

The opening paragraph points out the necessity of familiarity with proper medical terminology. Following this is a general outline of the structure of the human body, with a table of nomenclature. The emphasis is somewhat plebeian in that the common names for the parts of the body receive first place, while the BNA terms are in smaller print. This is true both in the line drawings and in the text. In the tables, the positions of the terms are reversed.

Each body region, as the chest, the cardiovascular system, the nervous system, the bones, the muscles, the endocrine glands, and the genitourinary system, receives brief consideration. Contrast media and the medical terms for the examinations in which they are used are listed in alphabetical sequence.

Despite the small size of the book, the author does find a place for Stumpf's trick of visually simulating heart action by using a properly lined sheet of tracing paper which can be moved over a black and white reproduction of a roentgen kymogram. Diagrams are used to teach the terminology for roentgen beam direction and patient positions. It is to be regretted that the first and second obliques with their interesting German names of the *dueller* position and the *boxer* positions are not included. The book closes with thirty-four sample normal roentgenograms.

The format, the printing, and the quality of the paper are all good, though the volume would require rebinding for permanent use. One application to be suggested is for students in literary schools taking courses in scientific German. This book would give them, in simple context and easy German, the visual identification of body parts with their common popular names.

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ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Importance of Accurate Diagnosis by Cerebral Angiography in Cases of "Stroke." Robert A. Kuhn. J.A.M.A. **169:** 1867–1875, April 18, 1959. (25 Franklin St., Morristown, N. J.)

It is pointed out that an exact anatomic diagnosis in cases of "stroke," or cerebrovascular disease, is essential for proper medical management. With significant frequency, the symptoms of cerebral thrombosis can be reversed or arrested by anticoagulants, atheromatous occlusions of the carotid artery can be corrected and intracranial hemorrhage can, upon occasion, be checked.

The most potent factor contributing to the recent revolution in diagnosis and treatment of cerebrovascular disease has been the development of safe cerebral angiography. There is, for example, no other sure way known at present for distinguishing patients with cerebral artery disease from those with cervical carotid disease or with more unusual causes of stroke, such as brain tumor. The author has carried out this procedure in over 100 patients with stroke of all kinds and had no morbidity or mortality attributable to the examination. He uses 50 per cent Hypaque.

Six cases are presented and discussed in which it was felt the anatomic diagnosis aided in the proper clinical management of the patient. The series illustrates the nonspecificity of clinical diagnosis, in contrast to the results obtainable by serial cerebral angiography. The author feels that the latter procedure should be considered a vital and routine part of the treatment of patients with hemiplegia or other manifestations of "stroke," with or without intracranial bleeding.

Six roentgenograms. GEORGE A. SHIPMAN, M.D.
Staten Island, N. Y.

The Angiographic Study of Carotid Insufficiency and Cerebral Ischemia. Marvin M. Keirns and John E. Whiteleather. Am. J. Roentgenol. **81:** 929–944, June 1959. (J.E.W., Baptist Memorial Hospital, Memphis, Tenn.)

Between January 1951 and May 1958, cerebral angiography was performed in 1,535 patients at the Baptist Memorial Hospital, Memphis, Tenn. This includes 626 consecutive examinations in which the carotid bifurcation, as well as the intracerebral vessels, was routinely visualized. Equipment alterations, permitting demonstration of the neck vessels on every cerebral angiogram, were initially made to improve the diagnosis of carotid occlusion. A study of the much broader problem of stenosis was an outgrowth.

Stenosis of the carotid artery, of varying degree, was found three times more frequently than tumor, five times more frequently than aneurysm, and fifteen times more frequently than arteriovenous anomaly. Carotid insufficiency is often clinically indistinguishable from tumor, intracerebral hemorrhage, cerebral embolus, or "idiopathic cerebral atrophy." The process starts surprisingly early in middle life. It was observed in patients as young as thirty-one years and undoubtedly often exists for years before the diagnosis is made.

In the early or developing stage, carotid insufficiency produces a variety of minimal symptoms: headache, mental disturbances, transient paresthesias, or speech difficulties that are usually ignored or casually dismissed. Yet even at the present status of vascular surgery, some of these patients can be successfully treated before a complete occlusion occurs. This is possible only if the disease process is suspected and the patient referred for angiography early. This examination should be carried out on patients of all types and all ages, including those who have just suffered an acute cerebrovascular accident. In the authors' experience, this policy has proved safe.

Locations where stenosing plaques have been observed are those where complete occlusion most frequently occurs. Undoubtedly, stenosis leads to occlusion, and treatment of the stenosing plaque prevents the later occlusion. Four types of stenosing disease have been observed, each with its own clinical and pathologic characteristics: (1) solitary constriction at the bifurcation of the common carotid artery; (2) localized constriction in the carotid siphon or in the anterior or middle cerebral arteries; (3) multiple small plaques in secondary and tertiary cerebral arterial branches; (4) uniformly narrow, sparse vessels throughout the brain without any definite identifiable plaques.

Correlation between carotid and cerebral vascular stenosis and atrophy was established.

Thirty-three roentgenograms; 5 tables.

Patent Primitive Trigeminal Artery Studied by Cerebral Angiography. Georg-Fredrik Saltzman. Acta radiol. **51:** 329–336, May 1959. (Serafimerlasarettet, Stockholm, Sweden)

The author describes and discusses 8 cases of patent primitive trigeminal artery. In each instance the carotid-basilar anastomosis was of the primitive trigeminal artery type: the superior cerebellar arteries on both sides received their blood supply, or at least the greater part of it, through the anastomosis; furthermore, a vertebral artery was present and had as its main task the supplying of the inferior posterior cerebellar artery. In spite of these common features, two different types of the anomaly were noted. In one type, the entire vertebral artery system distal to the anastomosis was supplied through this communication and there was a poor filling of the posterior communicating artery. In the second type, the anastomosis was mainly supplied by the superior cerebellar artery on both sides, while the posterior cerebral artery received its blood through the posterior communicating artery.

According to the author, it seems that a patent primitive trigeminal artery can give rise to subarachnoid hemorrhage. He discusses the clinical significance of this anomaly and the need for a thorough angiographic examination if a surgical closure of the anastomosis or ligation of a carotid artery is to be undertaken.

Eleven roentgenograms. JULIAN O. SALIK, M.D.
Baltimore, Md.

The Roentgen Diagnosis of Cerebrospinal Fistulas and Pneumatoceles, Especially of the Anterior Cranial Fossa. C. Brandt. Fortschr. a. d. Geb. d. Röntgenstrahlen **91:** 182–195, August 1959. (In German) (Jupiterweg 5, Solingen-Ohligs, Germany)

In general, a distinction is made between spontaneous

and symptomatic cerebrospinal fistulas. Spontaneous occurrence is rare. Symptomatic cases are grouped according to their etiology; of the author's 72 cases, 3 were due to increased intracranial pressure, 1 to a tumor; 3 to osteomyelitis; 60 to fractures. Five were postoperative.

Cerebrospinal rhinorrhea may follow cranial trauma within a few days, weeks, months, or even years. It may be due to fractures of the ethmoids, particularly the cribriform plate, or the posterior wall of the frontal sinus. The discharge may be constant or intermittent.

In connection with cerebrospinal fistulas, pneumatoceles are mentioned. According to their location, these can be grouped as intracranial or intracerebral. Their roentgen localization is relatively easy. Subdural air shows marked motility on the postero-anterior and anteroposterior films; subarachnoid air is less mobile, with a fine, linear sometimes patchy distribution. Cisternal air is basilar in location. The air in the epidural space (between dura and bone) exhibits almost no mobility and is demonstrable for a short period only. That in the ventricular system is of typical form and the diagnosis causes no difficulty. The intracerebral pneumatoceles appear late after trauma, and are demonstrated on the roentgenogram as translucent defects, mostly in the frontal region. Often a defect will show a triangular narrowing at its base, pointing to the site of communication.

Operative repair is definitely indicated in cases of cerebrospinal fistulas and pneumatoceles following fractures of the anterior fossa, because of the constant danger of meningitis and the complications of the increased intracranial pressure. The preoperative roentgen diagnosis is very important. In the author's clinic, stereoscopic films are made in addition to the regular skull and sinus films. If the patient's condition does not permit an examination of this extent, spot-films with intensification and a fine-focus tube are made under fluoroscopic control. The crista galli should be scrutinized carefully, because this region is the most common site of fistulas.

To recognize abnormal changes, a knowledge of the normal anatomy is essential. A tomogram obtained with sagittal entrance of the rays is helpful in recognition of the traumatic changes in the anterior and posterior wall of the frontal sinus and also of the orbital brim. With the aid of bitemporal tomograms, the walls of the frontal sinuses, the presence of bony spicules and of depressed fragments, the ethmoid sinuses, and their fistulas can be visualized. Sometimes bilateral comparison films are necessary. In 82 per cent of the author's series of cases a preoperative roentgen diagnosis was made.

Twenty-three roentgenograms; 2 tables.

ILONA D. SCOTT, M.D.
Lewisburg, W. Va.

A Method for Localizing the Pineal Gland on Anteroposterior Projections. John R. McLaren. Am. J. Roentgenol. **81:** 945–952, June 1959. (Emory University School of Medicine, Atlanta, Ga.)

Not infrequently the radiologist is asked to evaluate roentgenograms of the skull for the position of the pineal gland. Unfortunately, the patient often is unable to cooperate or cannot be satisfactorily immobilized and some rotation is present on the roentgenogram. The author describes a method in which a line determined by two mid-sagittal structures is used to localize the pineal gland in anteroposterior views of the skull.

On both anteroposterior and Chamberlain-Towne roentgenograms of the skull a line connecting the midpoint of the dorsum sellae to the lambda and a line connecting the opisthion to the bregma pass through the normally placed pineal gland whether or not there is any rotation. If the pineal gland is abnormally placed, its position relative to the reference lines is unchanged with rotation, provided the position in the lateral view is within normal limits.

On postero-anterior roentgenograms, no anterior landmark could be found which fulfills the necessary criteria. These all shifted farther with respect to the pineal gland than did the posterior landmark, giving the appearance of a pineal shift.

Due to a normal variation in the position of the pineal gland in the anteroposterior diameter of the skull, a normal range on rotated anteroposterior skull roentgenograms must be defined which will increase with the degree of rotation. When the extent of rotation is slight, this range is only 1 or 2 mm.; hence, small shifts of the pineal gland on rotated anteroposterior skull roentgenograms must be evaluated.

Since the pineal gland can be adequately localized on rotated anteroposterior roentgenograms of the skull, these can be used to advantage for better visualization of faintly and indistinctly calcified pineal glands.

Ten roentgenograms; 2 tables.

Relationship between Fahr's Disease and Hypoparathyroidism: Case Report and Clinical Data. I. M. Stoppa and G. Farinet. Radiol. med., Milan **45:** 316–332, April 1959. (In Italian) (Istituto di Radiologia dell'Università, Turin, Italy)

In 1930, Fahr described neurologic disturbances related to "idiopathic, not arteriosclerotic, intracerebral, vascular calcifications" (Centralbl. f. allg. Path. u. path. Anat. **50:** 129, 1930). Under the name of Fahr's disease, however, are being described calcifications of the basal ganglia which in about half the patients are associated with demonstrable hypoparathyroidism, as in the 2 cases reported in this paper. The authors suggest that the eponym Fahr's disease be reserved for cases of basal ganglia calcification associated with neurologic disturbances but without signs of hypoparathyroidism.

Thirteen roentgenograms; 1 table.

E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

A New Method of Radiographic Exophthalmometry. B. W. A. Leeming. Brit. J. Radiol. **32:** 539–546, August 1959. (Public Hospital, Wellington, N. Z.)

Exophthalmos is usually measured in a relative sense, *i.e.*, the distance that the anterior margin of the cornea stands in front of the compressed skin over the most lateral part of the orbital margin, with the eyes looking forward. The author describes a new radiographic method based on measurement of absolute exophthalmos which is the degree of abnormal protrusion of the eye from its socket. Thus, if the distance of the cornea from a fixed reference point along its axis of movement is measured and the distance between this point and the anterior limit of the cornea in its normal position is subtracted, the difference is the amount of exophthalmos. Since precise measure-

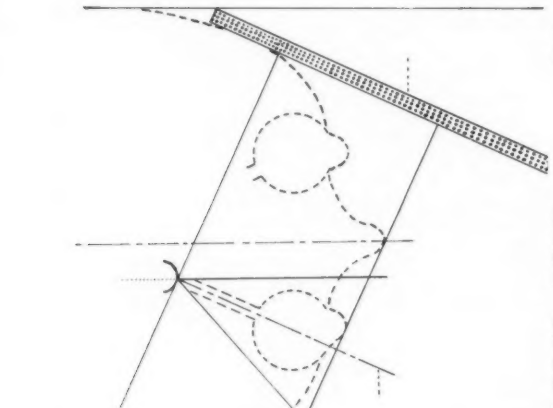

Diagram illustrating technic of exophthalmometry (Leeming).

ments of orbital depth in normal subjects are not available at the present time, the method described is more applicable to measuring changes in the degree of exophthalmos.

The radiographic technic consists in placing the head in a true lateral position and passing a beam of x-rays perpendicular to the plane of the axis of the uppermost orbit so that the central ray passes through the midpoint of this axis. In order to avoid distortion the film is placed perpendicular to the x-ray beam. The angle the central ray makes with the sagittal plane of the head is 22 1/2 degrees, and the cornea is projected clear of the facial bones (see accompanying diagram). The most forward point on the corneal image forms the anterior limit of the orbital axis; the posterior limit is the anterior boundary of the sphenoidal sinus. The distance between these points is measured, corrected for magnification, and recorded. The progression or regression of the exophthalmos can be accurately recorded by repeating the examination after an appropriate interval.

Reliability of this technic was tested by evaluating (1) magnitude of errors due to false positioning of the head and (2) feasibility of obtaining exactly comparable films. False positioning produced possibly significant errors only when the orbit was turned toward or away from the tube. In practice, this error is easily avoided. Two separate measurements of each of ten normal subjects were highly comparable, indicating a high inherent accuracy in the method.

The original article should be consulted for description of a head-holding device, special filter, and exposure factors.

Seven figures, including 1 roentgenogram; 3 tables.

SAMUEL B. HAVESON, M.D.
Lynwood, Calif.

THE CHEST

Pulmonary Alveolar Proteinosis. Report of Two Cases. George F. Lull, Jr., James C. Beyer, John G. Maier, and Dwight F. Morss, Jr. Am. J. Roentgenol. **82:** 76–83, July 1959. (Fitzsimons Army Hospital, Denver, Colo.)

The authors present 2 new cases of pulmonary alveolar proteinosis, bringing to a total of 30 the number reported since 1953 [See following abstract for a more recent case; also paper by Plenk *et al.* in this issue of RADIOLOGY, page 928. The etiology of the condition is unknown, but it seems to be increasing in frequency. The histopathological changes consist of alveolar filling with proteinaceous material and proliferation of septal cells. There is little or no thickening of the interalveolar septa.

Clinically the manifestations are quite variable and may be complicated by a bacterial or fungal infection. In most patients there was a progressive dyspnea with cough, fatigue, chest pain, and loss of weight. The exact date of onset was difficult to establish.

The roentgen changes consist in a fine granular or "feathery" parenchymal density, soft in appearance, usually widely disseminated, resembling severe pulmonary edema in its radial distribution from the hili. The picture bears some resemblance to sarcoidosis, but hilar adenopathy is not a feature. The differential diagnosis roentgenographically includes pulmonary alveolar microlithiasis, stannosis, berylliosis, and hemosiderosis. The pulmonary lesions may remain unchanged over several months or years and be unrelated to changes in symptomatology. They may show progression with confluence of the parenchymal densities. Resolution is said to begin at the periphery and progress toward the hilus.

Therapeutic measures have been of little value except for secondary infections. Death appears to be the result of obliteration of the respiratory surface. Cor pulmonale was present in 2 of the previously reported cases. Since the mortality rate is high and treatment inadequate, the authors appeal for a vigorous search for the etiologic agent and development of a rational therapy.

Five roentgenograms; 2 photomicrographs.

NORMAN L. ARNETT, M.D.
Anaheim, Calif.

Pulmonary Alveolar Proteinosis. A Case Report with Unusual Clinical and Laboratory Manifestations. Francis B. Landis, Harold D. Rose, and Richard O. Sternlieb. Am. Rev. Respir. Dis. **80:** 249–254, August 1959. (VA Hospital, Wood, Wisc.)

Pulmonary alveolar proteinosis is characterized pathologically by deposition of a proteinaceous material in the alveolar spaces of the lung. It occurs chiefly in adults and is of insidious onset with slow progression of symptoms, which include cough, chest pain, dyspnea, and weight loss. Although the etiology is unknown, some noxious inhalant is suspected, since the lung is the primary site of the disease.

The roentgenographic findings are somewhat variable. They consist in patchy infiltrative densities occurring in the perihilar areas and medial bases, but the distribution is not necessarily symmetrical nor is it always limited to the perihilar regions. The diagnosis can therefore only be suspected in a patient with chronic disease involving the lungs.

In the case reported here, there was a history of three episodes of acute thrombophlebitis, two in the right leg and one in the left, before a third attack on the right resulted in referral to the hospital. None of the attacks of phlebitis was accompanied by any signs of pulmonary embolism. A year prior to admission the patient had an acute febrile illness with chills and chest pain, clinically diagnosed as pneumonia. A chest roentgenogram was not obtained at that time. Although the acute phase subsided in a few days, recovery was not complete. A persistent morning cough, productive of small amounts of sputum, developed, and the patient complained of easy fatigability, mild excursional dyspnea, anorexia, and a gradual weight loss of 40 pounds. Slight hemoptysis was noted on two occasions.

At the time of admission, the only pertinent chest findings were moist râles in the lung bases. Signs of thrombophlebitis were evident in the right leg. The liver was slightly enlarged. The admission chest roentgenograms revealed bilateral, soft, poorly defined infiltrations in both lower lung fields, more marked on the left. Some of these extended up to the perihilar areas. A month later a transient spread of the disease on the right side was noted, but this regressed, leaving the major change again on the left side. Right cervico-mediastinal lymph node biopsy was normal, but a biopsy of the lingula of the left upper lobe disclosed the distinctive features of pulmonary alveolar proteinosis.

In addition to the recurrent thrombophlebitis, unexplained laboratory findings included elevated serum lipid and cholesterol, hyperglobulinemia, and proteinuria. The greatest deviation from the normal occurred early, when the roentgenographic involvement of the lungs was most marked.

The patient worked as a filling station operator but denied undue exposure to noxious gases or sprays. He did admit an excessive alcoholic intake, with poor dietary habits, and had smoked one to two packs of cigarettes daily for thirty years. He improved while in the hospital and was discharged four months after admission. A month later he reported a gain of 13 pounds and a chest film showed slight clearing bilaterally.

[See paper in this issue of RADIOLOGY, by Plenk *et al.*, page 928; also preceding abstract.—Ed.]

One roentgenogram; 1 photomicrograph; 1 table.

JOHN H. JUHL, M.D.
University of Wisconsin

The Roentgenologic Evaluation of Systemic Lupus Erythematosus. Thomas Lee Taylor and Herman Ostrum. Am. J. Roentgenol. **82:** 95–107, July 1959. (T. L. T., 1001 Cedar St., Jacksonville, Fla.)

The authors have re-examined the roentgenograms in 23 proved cases of systemic lupus erythematosus studied at the Philadelphia General Hospital since 1946. Almost all of the patients were Negroes, and the usual age incidence was between twenty and forty years. The etiology, pathology, and clinical syndrome of the disease are discussed and the literature is reviewed briefly.

Definite roentgen changes were observed, reflecting acute or inflammatory changes in the pleura, lungs, and pericardium. The authors have evolved a system for pathologically correlating postmortem material with roentgenograms, using commonly accepted criteria as well as their personal experience obtained from correlation with the gross specimens. The changes visible in the chest roentgenograms which may suggest a correct diagnosis have been classified into four stages:

1. *Initial Acute Stage:* Bilateral moderate or massive pleural effusion; massive pericardial effusion; subpleural inflammation; perivascular inflammation; small areas of interstitial and segmental pneumonitis at the lung bases.
2. *Resolving Stage:* Minimal unilateral or bilateral pleural effusion: minimal to moderate pericardial effusion, with straightening of the left border of the cardiac silhouette but without widening of the heart base; small linear areas of "plate-like" atelectasis at the lung bases; areas of segmental atelectasis at the lung bases.
3. *Chronic Stage:* Unless the nephrotic syndrome is present the cardiac contour returns to normal or cor pulmonale develops. In some instances the outline of the pulmonary conus remains partly obscured by fibrosis which fills in the pericardial spaces around the conus. The pleural effusion may completely disappear. Fine pulmonary scars may be seen at the lung bases frequently associated with "tenting" of the pleura, or the lungs may appear clear. Multiple pulmonary infections occur.
4. *Exacerbation:* Pleural and pericardial effusions are limited by adhesions; fine linear densities are intermingled with small areas of interstitial pneumonia at the lung bases; basal areas of segmental pneumonitis occur; subpleural and perivascular inflammation is present.

In the differential diagnosis, the straightening of the left border of the heart is an important sign; it appears to be caused by small amounts of pericardial effusion. This sign often permits differentiation from Boeck's sarcoid, idiopathic cardiac hypertrophy, cor pulmonale with chronic infection at the lung bases, hyperthyroidism with secondary heart failure, and rheumatic heart disease. Periarteritis nodosa in the acute stage and systemic lupus erythematosus cannot be differentiated. In chronic periarteritis prominence of the pulmonary conus due to cor pulmonale may be distinguished in most instances from the straightening of the left cardiac border due to systemic lupus erythematosus. In hypothyroidism with pericardial effusion, this straightening may be indistinguishable.

Twelve roentgenograms.

NORMAN L. ARNETT, M.D.
Anaheim, Calif.

The Bronchographic Demonstration of the Normal and Pathologically Altered Excretory Ducts of the Mucous Glands, Also of Diverticula of the Bronchial Wall. G. Heim and W. Hoeffken. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 649–656, June 1959. (In German) (Medizinische Universitäts-Poliklinik, Cologne, Germany)

Since the advent of water-soluble media for bronchography, "niche-like" defects have frequently been

found in the bronchial wall. These vary in size, from tiny excrescences producing a fine tooth-like or fringe-like appearance up to diverticulum-like pockets as large as a pea. They have been attributed to a purulent bronchitis.

The authors of this article have studied these projections in 100 bronchograms, including 29 in cases of bronchial carcinoma, 41 in unspecific inflammatory diseases, and 15 in tuberculosis.

Fine fringe-like projections were found along the lower surface of the main bronchi or lower bronchi in 16 cases, and in the periphery, *i.e.*, in the segmental bronchi, in 14 cases; coarser irregularly placed "niche-like" projections in the main, lobar, and segmental bronchi were observed in 27 cases. Diverticulum-like pockets were seen only once. In 42 cases no projections could be demonstrated.

In studying the available surgical specimens, the authors found that these projections represented excretory ducts of mucous glands. The openings of the ducts were visible to the naked eye on the inner surface and ranged in size from 0.6 to 2 mm. On microscopic examination the tooth-like (fringe-like) projections on the lower surface of main and lobar bronchi showed no evidences of bronchitis and are regarded as normal. In the segmental bronchi, however, they represent pathologically enlarged ducts, since normally ducts of that size do not occur in the periphery. The coarse and irregularly placed "niche" formations are always the sign of a purulent bronchitis. The round, pocket-like projections are diverticula. They occur in older patients and are due to a degenerative or inflammatory weakness in the bronchial wall.

Five roentgenograms; 1 photograph; 5 photomicrographs. WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Interstitial Pneumopathy of Unknown Etiology (Hamman-Rich Syndrome and Micropolycystic Lung Changes). Edmondo Balestra. Radiol. med., Milan **45:** 443–465, May 1959. (In Italian) (Istituto di Radiologia dell'Università di Genova, Genoa, Italy)

One observation of interstitial pneumopathy with micropolycystic changes (including necropsy) and 4 cases of Hamman-Rich syndrome (2 proved at autopsy; 1 survival) are taken as a background for a review of the entire problem of interstitial pulmonary "fibrosis." The roentgen appearance is quite obvious in so far as there is demonstrated an involvement of the pulmonary "interstices" (peribronchial, perivascular, and subpleural connective tissue, in addition to the interalveolar septa), although even that may sometimes require tomographic evaluation. Further precision is not possible short of histologic examination. There is quite often a discrepancy between the roentgen and clinical findings, especially in the acute types, with dramatic symptomatology (dyspnea) but barely visible increase in lung markings.

Eleven roentgenograms. E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

Investigations on the Significance of a Few Important Roentgen-Diagnostic Procedures in Bronchial Carcinoma. H.-J. Eichhorn and W. Bohndorf. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 657–664, June 1959. (In German) (Deutsche Akademie der Wissenschaften zu Berlin, Berlin, Germany)

This paper is based on an analysis of 1,000 proved cases of bronchogenic carcinoma, of which 453 were subjected to thoracotomy. The examination for bronchogenic carcinoma involves two undertakings—the diagnosis and determination as to operability. The value of the various diagnostic procedures (bronchoscopy, bronchography, tomography, pneumomediastinum, kymography of the esophagus, angiography of the vena cava, pneumoangiography) depends to a great extent upon the location of the lesion. If it is in the main bronchus, bronchoscopy will be the most telling procedure, particularly because the biopsy then clinches the diagnosis. If the site is in the secondary bronchi or farther toward the periphery, bronchography assumes more importance by demonstrating a stricture or a bronchial obstruction. The differentiation between benign and malignant strictures may sometimes cause difficulties, but the percentage of error is small. In 69 per cent of the cases the diagnosis was made histologically by bronchoscopy and it was supported in 89 per cent by bronchography.

To settle the question of operability, fluoroscopy and radiography are of first importance. Relative or absolute contraindications, such as paralysis of the diaphragm, severe emphysema, dilatation of the heart, extension of the lesion into the esophagus, metastasis to the other hilus or the opposite lung can be easily recognized. In 53 per cent of the cases the possibility of surgery could thus be eliminated. Still, of the 453 tumors that were subjected to thoracotomy, 34 per cent were not resectable, for the following reasons: extension into the mediastinum (39 per cent), the thoracic wall (18.5 per cent), or the wall of large vessels or the heart (15 per cent); carcinomatous pleurisy (11 per cent); lentiform metastases in the pleura (6 per cent); extension into the area of the bifurcation (6 per cent); multiple abscesses, etc. (4 per cent). In the discovery of these signs of inoperability, tomography has been of some help, particularly if combined with pneumomediastinum, the gas being injected by the sacral route. Errors, however, have been frequent. When involvement of the vena cava was suspected, phlebography sometimes gave valuable information. In 10 cases in which a deformity or obstruction of the vena cava was shown by phlebography, carcinomatous involvement could be demonstrated in each instance. If the tumor is centrally located, kymography of the filled esophagus may add some information.

The sequence of examination is first fluoroscopy and radiography, then bronchoscopy. Further procedures depend on the location of the lesion. If it is more centrally located, the operability is evaluated by tomography and pneumomediastinum, esophageal kymography, cavography, and pneumoangiography; if the location is perihilar or peripheral, bronchography is indicated to secure the diagnosis.

Ten charts; 1 table.
WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

The Recognition of Shrinkage of the Lower Lobe of the Left Lung on the Plain Chest Film. F. Longin. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 665–678, June 1959. (In German) (Theaterstr. 17, Würzburg, Germany)

Changes in the left lower lobe of the lungs are often overlooked on the plain film because this lobe is hidden behind the heart and only a small part of it can be

seen in the left costodiaphragmatic angle. Fluoroscopy in various directions and oblique and lateral views are therefore of great importance. The suspicion of a shrinking process in the left lower lobe, such as an atelectasis, may be aroused by indirect signs, which are listed in the order of their frequency:

1. Displacement and distortion of the hilar shadow (the left hilus, which normally is one finger above the level of the right, is pulled down and deformed, often assuming the shape of a "V").
2. Displacement of the mediastinal organs to the left (either permanently or only during the process of "snuffing").
3. Lack of visualization of the lingula vessels on the plain film.
4. Streaky or spotty densities in the left lower lung (often caused by bronchiectatic shrinkage).
5. Displacement of the visible interlobar fissure dorsalward, as seen in the lateral view.
6. Arcade-like vessel shadows in the area of the left contour of the heart.
7. Straightening of the heart contour and covering of the aortic knob.
8. Emphysema of the left upper lobe.
9. Elevation of the left diaphragm.
10. Paravertebral triangular shadow.
11. Narrowing of the left half of the thorax.

Among 21 cases that were carefully checked, the author found 3 bronchial carcinomas, 10 cases of bronchiectasis, and 4 cases of shrinkage of the left lower lobe without bronchiectasis. He emphasizes the fact that great variations in the size of the left lower lobe may normally occur and that sometimes the differential diagnosis between a normal small lower lobe and a pathologically shrunken lobe cannot be made. Four cases are presented and discussed.

Eighteen roentgenograms; 2 drawings.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Hazards to the Host of Benign Intrathoracic Tumors. Richard H. Overholt and Wilford B. Neptune. J.A.M.A. **170:** 664–669, June 6, 1959. (New England Deaconess Hospital, Boston, Mass.)

Benign intrathoracic tumors carry essentially two hazards for the host: their relationship to vital intrathoracic structures and a possible cancer potential.

Correlation of clinical data, including the roentgen findings, permits a more accurate appraisal of these hazards than was formerly possible. If serial films over a period of years are available, some estimate of past growth may be obtained, but this is not a guide to future behavior. The more dense, clear-cut, and undisputed the x-ray evidence, the more ominous and threatening the lesion appears to many physicians. Actually, however, shadow density is usually inversely related to the degree of risk. Hazy, ill-defined, questionable areas of altered density represent lesions carrying a far more serious import than the circumscribed easy-to-see shadow.

Calcification has some bearing upon the problem. The presence of calcific deposits in *all parts* of an area of density is a reliable age indicator, pointing to a cessation of tumor growth when the calcium salts were precipitated. Thus, if a calcific tumor does not cause symptoms or interfere with function, it may remain indefinitely without serious risk.

In general, in view of the great advances made in thoracic surgery in the last three decades, the hazard (less than 1 per cent) of removal of these lesions is much less than the possible risk attendant upon their presence. Total biopsy at the same time constitutes curative therapy.

Nine roentgenograms; 4 drawings.

GEORGE A. SHIPMAN, M.D.
Staten Island, N. Y.

The Forms and Causes of Multiple Bone Formation in the Human Lung. K. Pollak. Fortschr. a d. Geb. d. Röntgenstrahlen **91:** 234–243, August 1959. (In German) (Gustav-Freytag-Str. 24, Erfurt, Germany)

To the 91 cases of multiple bone formation in the lung published in the last hundred years, the author adds another.

At present two types of bone formation in the lung are distinguished: tuberous and reticular.

Approximately 50 cases of the *tuberous form* have been reported. The most common location of the bony bodies is in the lower lobes, chiefly in the alveoli. In 7 cases some marrow was present in the bones. Any connection with the vessel walls and bronchi has been denied. Forty-eight of the patients had mitral disease with chronic congestion. The mechanism of the deposition of hemosiderin in the alveoli with subsequent chemical transformation into calcification is well understood, though it is not known why calcifications undergo a bony "metaplasia."

The bony bodies are rounded and vary in size from a pinhead to a pea. They are usually located in the mid lung fields and in the periphery and have a tendency to conglomeration; this and the lack of calcified hilar nodes should aid in the differentiation from miliary calcifications following tuberculosis. Also, a combination of mitral stenosis and miliary tuberculosis is very rare. The condition has been found in both sexes equally. The average age of the patient was about thirty-eight years.

The description of the *reticular type* of bone formation is based on the author's own case, in a 65-year-old man who had emphysema, hypertension, and repeated attacks of bronchopneumonia. Autopsy showed arteritis, cor pulmonale, and endocarditis. Multiple small bony deposits were palpable. Under the microscope true osteoid tissue was seen, with trabeculae and bone marrow. No connection could be found between the blood vessels and bronchi and the bony bodies. In the remainder of the lungs were recent and chronic bronchopneumonic infiltrates. The average age of the patients in this group is above forty; men predominate. Radiographic resemblance of the bony deposits to shell fragments is mentioned.

The author believes that repeated bronchopneumonia plays the same role in the development of reticular bone formation as does chronic congestion in the tuberous form.

Two photomicrographs; 2 tables.

ILONA S. SCOTT, M.D.
Lewisburg, W. Va.

Complete Bronchial Obstruction in Asthma: An Unusual Bronchographic Hazard. J. H. E. Carmichael and J. C. Woodrow. Brit. J. Radiol. **32:** 552–553, August 1959. (Broadgreen Hospital, Liverpool 14, England)

The authors report the case of a 27-year-old male

in whom a left bronchogram was obtained to exclude bronchiectasis. Neohydril was instilled by the cricothyroid route, and the findings were: (1) complete block of the main bronchus to the left lower lobe, (2) narrowing of the main bronchus to the upper lobe and all of the branches except that to the lingula, and (3) irregularity of the inferior aspect of the upper lobe bronchus suggesting edema of the mucosa. One week later, a normal right bronchogram was obtained and bronchoscopy revealed a completely normal bronchial tree. Subsequently, a repeat left bronchogram showed an essentially normal picture except for the presence of "mucous glands," probably due to bronchitis. The technic was unchanged in the last examination except for warming of the contrast material.

Further questioning of the patient revealed a history compatible with bronchial asthma of many years duration. The bronchial obstruction demonstrated by the first bronchogram apparently was the result of an acute asthmatic attack precipitated by instillation of cold Neohydril and a poorly heated radiographic room. Iodine sensitivity was ruled out, since there was no reaction during the subsequent performance of bronchography.

Two roentgenograms.

SAMUEL B. HAVESON, M.D.
Lynwood, Calif.

Roentgenologic Study of Primary Pleural Tumors. Importance of Stratigraphy in Differential Diagnosis from Pulmonary Cancer. G. D'Aste, E. Gandolfo, and G. Secondo. Radiol. med., Milan **45:** 209–233, March 1959. (In Italian) (Università di Genova, Genoa, Italy)

In the study of pleural tumors, and especially in their differentiation from pulmonary (bronchogenic) carcinomas, there is a definite advantage in using transverse stratigraphy. Nevertheless, even conventional procedures may help, as can be seen from the following table:

	Pleural Tumors	Pulmonary Cancer
Shape	Rounded or lobulated	Rounded or infiltrating
Location	More often peripheral	More often central
Margins	Regular or irregular	Almost always irregular
Opacity	Homogeneous	Almost always nonhomogeneous
Hilar lymph nodes	Rarely infiltrated	Almost always infiltrated
Mediastinum	Often shifted toward the unaffected side	Often shifted toward the affected side
Bronchi and vessels	Rarely displaced	Often displaced, narrowed, and occluded
Atelectasis	Circumscribed; always of the compression type	Diffuse
Effusion	Constant in the diffuse type of pleural tumor; seldom in the circumscribed form	Usually absent
Metastases	Late and rare	Early and frequent

Twenty-eight roentgenograms; 1 table.

E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

A Contribution to the Differential Diagnosis of Space-Occupying Mediastinal Processes. J. Lissner. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 679–686, June 1959. (In German) (Medizinische Universitätsklinik, Frankfurt am Main, Germany)

In recent times the differential diagnosis of space-occupying processes of the mediastinum has been considerably refined by special methods of examination, such as tomography, angiography, kymography and pneumomediastinum. Three cases are presented.

The first patient was a 23-year-old woman who had experienced pain of angina-like character for one year. An x-ray examination showed what looked like a huge enlargement of the heart, suggesting an exudative pericarditis. Puncture yielded a large amount of clear fluid. On subsequent punctures, however, the fluid became cloudy and finally putrid. Fluid levels could be demonstrated. As the patient's condition grew worse, surgical drainage was attempted. The surgeon found a huge abscess, which seemed to be anterior to the heart. Autopsy showed a large cystic teratoma in the lower anterior mediastinal space. Special methods of examination (angiography) probably would have established the diagnosis.

In the second case the differential diagnosis between tumor and aneurysm was the problem. A 73-year-old man had a round mass in the upper mediastinum, with marginal shell-like calcific deposits. Tomography showed a normally shaped aortic arch, which, though unusual for an aneurysm, does not exclude the possibility. Clinically the patient had bloody sputum and difficulty in swallowing. A diagnosis of an aneurysm plus a tumor was made. At autopsy a large hemangioendothelioma of the thyroid gland was found. No aneurysm was present. The shell-like calcifications were in the tumor. Again angiography and pneumomediastinum would have helped in the diagnosis.

The third patient was a 55-year-old woman who had a marked widening of the upper mediastinum toward the right side. The lateral film revealed various calcifications in the mass. As the Wassermann reaction was positive, an aneurysm was considered, but tomography with pneumomediastinum showed that the aorta was normal and that the tumor extended up into the neck toward the thyroid gland. Since the metabolism rate was high (plus 71 per cent), the diagnosis of a calcified struma was made, and this was later confirmed.

Ten roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

THE HEART AND BLOOD VESSELS

Thoracic Aortography in Infants and Children. Robert S. Cartwright and S. Richard Bauersfield. Ann. Surg. **150:** 266–274, August 1959. (S. R. B., University of Pittsburgh School of Medicine, Pittsburgh, Penna.)

Experience with thoracic aortography in 92 infants and children is presented. For comparative purposes the series was divided into two groups. The first consisted of 25 patients in whom thoracic aortography was performed by various technics during the years 1953 and 1954. Sixteen satisfactory and 7 unsatisfactory aortograms were obtained in this group; there were 2 deaths and 2 examinations were not completed

because of untoward reactions. In the remaining 67 patients, 68 aortograms were obtained. In 15, the right carotid, left brachial, or left axillary approach was used, with a single death; 53 examinations were done by the left carotid approach with no mortality and but 1 unsatisfactory study. It is this latter technic which is preferred by the authors. The catheter in the left common carotid is advanced almost to the junction with the aorta and secured with a ligature before injection. (For suspected aortopulmonary fenestration and aortic sinus fistulas it is preferable to pass a catheter through the right common carotid into the proximal aorta.) The opposite carotid is occluded by manual compression during injection of 35 per cent Miokon (1 c.c./kg.). General anesthesia is used.

Indications for the procedure in the series reported were the presence of a left-to-right shunt without the typical signs of a patent ductus, signs of an aortic sinus fistula, aortopulmonary fenestration, coarctation, and a vascular ring.

In the entire series definitive diagnoses were made in 34 patients. In 24 of these the defect was surgically corrected, and in 7 correction will be undertaken later.

Eight roentgenograms; 4 tables.

ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Retrograde Aortography in Corrected Transposition of the Great Vessels. Otto G. Thilenius, Eleanor Lu, Francesco S. Tolone, and Donald E. Cassels. J. Dis. Child **98:** 221–226, August 1959. (Division of Pediatrics, University of Chicago Clinics, Chicago 37, Ill.)

The term "corrected transposition" applies to the situation when the aorta and the pulmonary artery arise from their proper physiological ventricles, but the ventricles are themselves anatomically transposed. In this case, the right ventricle has the internal anatomical characteristics of the left ventricle, and the left ventricle those of the right. The radiological characteristics of this deformity have been described elsewhere in the literature. The authors proceed to describe the typical appearance of corrected transposition as demonstrated by retrograde aortography.

In corrected transposition, the cardiac silhouette shows a left heart border either unusually straight or slightly bulging in the area normally occupied by the pulmonary artery. A catheter in the ascending aorta shows displacement to the left heart border. The aorta arises far to the left of its normal origin. There may be a right or a left aortic arch, but in either case, the root of the aorta appears in the same typical lateral position. The aortogram also demonstrates the abnormal pattern of the coronary arteries, accompanying their proper anatomical ventricles. The left coronary artery, with its anterior descending and circumflex branch, is on the right side, and the right coronary artery, with its posterior descending and circumflex branch, is on the left.

Although corrected transposition is probably more often diagnosed by cardiac catheterization or angiocardiography, the retrograde aortogram appears superior to the angiogram, since it shows clearly the abnormal position of the root of the aorta, uncovered by shadows due to filling of the other chambers of the heart and also demonstrates the typical inverted pattern of the coronary arteries.

As corrected transposition is at times associated with marked cyanosis, differential diagnosis has to be made between complete and corrected transposition, as the surgical considerations are different. The position of the aortic route differentiates the two conditions. In complete transposition, the aorta is anterior but does not arise along the left heart border. Another condition of differential diagnostic interest is a hypoplastic pulmonary artery with an associated wide aorta arising in normal position from the normal left ventricle. The abnormal margin of the aortic root as demonstrated by angiocardiography in this case is due to the abnormal position of the heart in the chest.

The authors conclude that, when the diagnosis of corrected transposition needs confirmation, the frontal retrograde aortogram appears to be nearly pathognomonic.

Eight roentgenograms; 1 photograph; 1 diagram.

JOHN P. FOTOPOULOS, M.D.
Evanston, Ill.

Coronary Arteriography. J. Stauffer Lehman, Randal A. Boyer, and Fred S. Winter. Am. J. Roentgenol. **81:** 749–763, May 1959. (230 N. Broad St., Philadelphia 2, Penna.)

The authors describe their experiences with coronary artery visualization, employing catheter thoracic aortography, cardiac ventriculography, suprasternal thoracic aortography and its component suprasternal transaortic coronary arteriography, and cardiac arrest coronary arteriography. The coronary arterial and aortic opacifications resulting from each of these procedures are tabulated.

While cardiac ventriculography can effect coronary artery opacification with considerable frequency, this procedure has the disadvantage of dense opacification of the left ventricular cavity, which may obscure portions of the coronary artery system, since the injected medium is somewhat diluted when it reaches the coronary ostia. Cardiac ventriculography is not without hazard, and the authors do not believe it has proved itself to be the "choice" technic for coronary arteriography.

Suprasternal needle puncture procedures (suprasternal thoracic aortography and suprasternal transaortic coronary arteriography) are likewise not without danger. The possibility of intramural aortic injection of the contrast medium and of aortic bleeding must not be overlooked. In a percentage of their examinations, the authors were not successful in penetrating the aorta by the needle. It is their conviction that there is need for further experience with such needle-puncture procedures before their usefulness can be fully established.

In the authors' opinion, catheter thoracic aortography appears to be the most efficacious method of delivering a relatively undiluted, high-concentrate radiopaque substance to the coronary ostia in a quantity sufficient to obtain good coronary artery visualization. The ability to deposit the medium at a predetermined level in the ascending aorta, with regularity, is of considerable advantage. The risks involved in this procedure are principally those related to malposition of the catheter tip and those incident to repair or closure of the artery through which the catheter is introduced.

Cardiac arrest coronary arteriography seems to merit further investigation. The potential hazards of inducing a period of cardiac asystole are as yet indeterminate. Thus far, the authors' experience would suggest that this procedure may be of considerable worth

in consummating satisfactory coronary artery visualization, but they are not unconcerned as to its possible dangers.

Other technics of coronary arteriography, including aortic occlusion coronary arteriography, and cardiac arrest coronary arteriography plus aortic balloon occlusion, are discussed.

Fourteen roentgenograms; 2 diagrams; 4 tables.

Calcification of the Coronary Arteries. David H. Blankenhorn and David Stern. Am. J. Roentgenol. **81:** 772–777, May 1959. (1200 North State St., Los Angeles 33, Calif.)

Sixty-one of 76 adult human hearts examined roentgenographically postmortem exhibited calcific lesions in the coronary arteries. Forty-one of the autopsied patients were selected at random from the autopsy population over one year of age. To this number, 32 consecutive subjects over one year of age were added. Thirty-one hearts also had calcification at another site, and in 7 extracoronary calcification predominated. Two of the 76 hearts showed only valvular calcification.

Coronary calcifications were the most frequently encountered intracardiac radiopaque lesions and were more commonly present than absent in patients over forty years of age. Four patterns of calcification could be distinguished: (1) punctate, (2) blocky (*i.e.*, oblong or linear, sufficiently large to outline the vessel in which it occurred), (3) double, and (4) incomplete double. The most common calcific coronary lesions were 1-, 2-, and 3-mm. punctate densities, occurring in groups of two to four in the proximal portions of the artery.

Five roentgenograms; 5 tables.

Experimental Coronary Arteriography. L. Di Guglielmo, V. Baldrighi, F. Coucourde, and A. Schifino. Radiol. med., Milan **45:** 401–419, May 1959. (In Italian) (Istituto di radiologia medica dell'Università di Pavia, Italy)

Rousthöi, in 1933, appears to have been the first to perform coronary arteriography experimentally (with Thorotrast); all 5 of the dogs undergoing the procedure died. In the series reported here, a total of 223 instances of visualization of the coronaries were obtained in 73 dogs. The technic was that described by Radner (modified by Jönsson *et al.*, and by the present authors): With the dog lying on its left flank, under general anesthesia, the largest possible catheter was inserted through the right common carotid and advanced into the ascending aorta under fluoroscopic control as far as the semilunar valves; 25 to 40 c.c. of 70 per cent iodinated contrast medium (up to 1.5 c.c. of contrast material per kg.) was injected within one second (Dos Santos compressor), and 4 to 12 serial exposures were made at the rate of two per second. In all instances, arterial pressures were registered with a Sanborn electromanometer, connected to a catheter inserted into the descending aorta through a femoral artery. Electrocardiograms (before, during, and after injection) were taken in 32 cases. In a few dogs, the coronary blood flow was determined during the injection, by a thermo-electric probe placed in the venous coronary sinus.

On the basis of their experience, it seems to the authors that improvement in coronary visualization can be achieved by (1) giving adenalin-like substances, (2) using intrapulmonary hypertension, which slows down the circulation time, (3) associating the previous two procedures, and (4) occluding the ascending aorta (with an inflatable balloon) at the moment of injection. The method appears to be of value not only for anatomic, but also for physiologic studies. While fatalities still occurred, the risks are somewhat lessened: 2 dogs survived four successive procedures, and 17 dogs survived three injections, without demonstrable damage. The procedure is still far from a clinical stage; in fact, it is questionable whether it will ever be performed on a large scale.

Fourteen roentgenograms; 2 graphs.

E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

A Comparison of Techniques for Visualization of the Coronary Arteries. Jacob I. Fabrikant, William G. Anlyan, George J. Baylin, and Robert B. Trumbo. Am J. Roentgenol. **81:** 764–771, May 1959. (J. I. F., The Johns Hopkins Hospital, Baltimore 5, Md.)

Various technics of coronary arteriography were compared in dogs with myocardial infarcts secondary to ligation of the left anterior descending coronary artery.

Methods for Contrast Visualization: Comparisons were made of (1) time and dosage factors in chemically induced cardiac arrest; (2) the filling of the arterial tree in the moving *versus* the arrested heart; (3) various radiopaque media in different concentrations; (4) the preferred location of the catheter tip; (5) manual injections *vs.* automatic injector; (6) optimum pressure values for injection; (7) single table-top roentgenography versus the Schönander unit roentgenographic machine; (8) exposure time during the various procedures.

Methods for Evaluating Myocardial Damages: Comparisons were also made of (1) electrocardiographic tracings taken before, during, and at periodic intervals after each procedure; (2) serum transaminase levels determined before and after each procedure; and (3) detailed histologic examination of the heart carried out at autopsy, with particular attention to evidence of fresh damage (due to the last arteriography) superimposed on the old myocardial infarcts.

The injection of 30 c.c. of 50 per cent Hypaque with an automatic injector through an intra-arterial catheter with the tip located at the junction of the brachiocephalic artery and the ascending aorta consistently produced adequate visualization of the coronary arterial tree. The technic was improved by the use of temporary acetylcholine cardiac arrest. Acetylcholine cardioplegia provided a safe, transient asystole; reversion to normal occurred within two minutes.

Electrocardiographic monitoring, serum transaminase determinations, and histologic examinations disclosed no significant alterations following induced arrest and arteriography. Because of its alleged capacity for secondary damaging effects, the use of Thorotrast should be restricted.

There apparently was no added hazard to the use of coronary arteriography and acetylcholine arrest in dogs with myocardial infarcts. Such experimentally induced lesions were depicted clearly.

The authors propose the employment of coronary arteriography as a special diagnostic procedure in patients with coronary occlusive disease. The selection of candidates for direct coronary artery surgery *versus* indirect methods of increasing myocardial blood

flow may be based on such arteriographic studies. Ten figures, including 5 roentgenograms.

Electronically Controlled Coronary Arteriography. Harold C. Urschel, Jr., and Earl J. Roth. Ann. Surg. 150: 275–289, August 1959. (H. C. U., Massachusetts General Hospital, Boston, Mass.)

A method of selective coronary arteriography for the laboratory animal is described which uses a minimum of contrast medium and a single x-ray exposure, thereby reducing greatly the hazards of the procedure. Electronic control eliminates the variables inherent in any manual operation.

A catheter is placed in the proximal aorta *via* the carotid artery and 1 c.c. of 50 per cent Miokon is injected in early diastole at 5 to 10 lb./in.^{2} pressure. Partial and total artificial obstructions in the coronaries were produced and easily demonstrated. The time of the injection was controlled electronically from the electrocardiograph.

The amount of medium used, length of time of injection, as well as the time in relation to the cardiac cycle, the pressure of injection, and the concentration of medium were all varied until the optimum combination was found. The apparatus is described in detail.

The procedure has not yet been tried in man, but the authors predict that 2 to 4 c.c. of the medium will be adequate for good coronary visualization.

Four roentgenograms with accompanying diagrams; 1 photograph; 4 drawings. ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Observations on the Systemic Venous Collateral Circulation in Portal Hypertension and Other Morbid States Within the Thorax. Robert Schobinger, Philip Cooper and Louis M. Rousselot. Ann. Surg. 150: 188–195, August 1959. (VA Hospital, Bronx, N. Y.)

Hitherto, studies on portal hypertension have in the main been focused upon the anatomy, pathology, and altered hemodynamics of the *portal* venous bed. The present authors report observations on the systemic collateral circulation in portal hypertension as obtained by injection of contrast material directly into the medullary cavity of a rib. Under normal conditions, the medium passes rapidly into one or two intercostal veins, which drain into the hemiazygos vein posteriorly. This latter venous channel joins the azygos vein, which can be identified up to its point of junction with the superior vena cava. The caliber of the veins remains relatively uniform, and the transition from one to the other is smooth and well delineated.

In portal hypertension the venous pattern is more complicated. An increased number of intercostal veins are opacified and sometimes collaterals are seen along the thoracic and abdominal walls. Knob-like prominences are present at the junctions of the major tributaries. The azygos and hemiazygos veins are poorly seen, except for the bulb of the azygos, because of the high flow rate with these veins. The internal vertebral plexus and ascending lumbar veins may be opacified. Occasionally an accessory hemiazygos vein and collaterals in the mediastinum may be seen.

In cardiac failure and block of the superior vena cava, the azygos and hemiazygos are well visualized. The internal vertebral plexus and ascending lumbar veins are at lower levels than in portal hypertension.

The authors believe that the procedure which they describe may be of considerable help in a patient with a gastrointestinal hemorrhage, since a normal venous pattern would rule out esophageal varices as the source of bleeding. It can also be used to demonstrate improvement following a caval shunt.

Eight roentgenograms; 4 photographs; 3 diagrams.
ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Postamputation Radiographic Evidence for Small Artery Obstruction in Arteriosclerosis. Edward A. Edwards. Ann. Surg. 150: 177–187, August 1959. (Peter Bent Brigham Hospital, Boston, Mass.)

Thirteen amputated lower limbs from patients with arteriosclerosis, 4 of whom were diabetic, were studied radiographically following perfusion of the arteries with an opaque medium. The patients ranged in age from fifty-seven to eighty-nine. Extensive occlusion of the smaller arteries was observed with no difference in this respect between diabetics and nondiabetics. Collateral paths were filled, and in 2 instances arteriovenous communications were noted. The arteries particularly involved were the branches of the medial and lateral aspects of the heel and the free borders of the first and fifth toes.

Four lower and two upper extremities of young subjects, amputated because of proximal nonvascular disease, were also examined. The vessels in these were presumably normal, and the films offered confirmation of the pattern of the arteriosclerotic occlusions.

Eight roentgenograms; 9 diagrams.
ZAC F. ENDRESS, M.D.
Pontiac, Mich.

Management of Arteriosclerosis Obliterans of the Extremities. Fay A. LeFevre, Cahid Corbacioglu, Alfred W. Humphries, and Victor G. deWolfe. J.A.M.A. 170: 656–661, June 6, 1959. (Cleveland Clinic Foundation, Cleveland, Ohio)

A follow-up study of 500 cases of arteriosclerosis obliterans indicates that 75 per cent show little progression of the disease over a five-year period. This makes the assessment of medical management difficult.

For the 25 per cent of patients requiring more than conservative treatment, angiography was considered indispensable, as it is the only means of localizing segmental occlusion. The authors believe that all patients with severe ischemia with or without gangrene should have the benefit of this procedure.

Prior to vascular surgery, the disease is estimated to have been 55 per cent fatal within three years. In 308 patients undergoing arterial grafting, there was about 7 per cent mortality; 91 per cent of the patients were asymptomatic at six months to four and one-half years follow-up.

This emphasizes the necessity of early and accurate diagnosis. Only rarely were angiographic findings misleading as to the technical feasibility of surgery. In 1,000 angiograms the morbidity did not exceed 0.1 per cent and there were no fatalities.

Eight figures, including 2 roentgenograms; 3 tables.
GEORGE A. SHIPMAN, M.D.
Staten Island, N. Y.

Arteria Lusoria. Aldo Bigo and Roberto Dall'Acqua. Radiol. med., Milan 45: 234–249, March 1959. (In Italian) (Ospedale Mauriziano, Turin, Italy)

In 1789, Bayford described under the designation

dysphagia lusoria the disturbances of deglutition allegedly resulting from pressure upon the esophagus by the right subclavian artery, which (in the absence of an innominate trunk) had an anomalous trajectory because of its separate emergence from the aortic arch (usually distal to the left subclavian). In 1926, Arkin proposed the name arteria lusoria for the anatomical malformation itself (Wien. Arch. f. inn. Med. **12**: 385, 1926). The roentgenologic feature of this condition, first described in 1936 by Kommerell (Fortschr. a. d. Geb. d. Röntgenstrahlen **54**: 590, 1936), consists of pressure defects visible on the esophagogram. The location of these defects varies with the particular trajectory of the anomalous artery. The most typical appearance is that in which the esophagus resembles somewhat the overriding fragments in an oblique fracture of a long bone. Others have called this the bayonet deformity.

During the performance of about 2,000 esophagograms, the authors have diagnosed arteria lusoria in 10 patients (0.5 per cent of the entire series). In all it was a chance finding, none of the number having any symptoms referable to the esophagus. While the relationship between this developmental abnormality and the assumed dysphagia is very tenuous, recognition of arteria lusoria is important for the differential diagnosis of pressure defects in the esophagogram.

Twenty-eight roentgenograms; 3 drawings.

E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

THE DIGESTIVE SYSTEM

Gastric Volvulus. F. Chiariotti and G. Puricelli. Radiol. med., Milan **45**: 353–372, April 1959. (In Italian) (Ospedale di Circolo di Busto Arsizio, Italy)

On the basis of 5 observations (2 of chronic organoaxial gastric volvulus, 1 of intermittent mesentericoaxial gastric volvulus, 1 of intermittent partial mesenterico-axial gastric volvulus, and 1 of chronic organoaxial volvulus in the presence of a congenital hiatus hernia), the authors review the entire problem of gastric volvulus, and re-evaluate the roentgen findings.

Fourteen roentgenograms.

E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

Hodgkin's Sarcoma of the Stomach. E. de Arzúa Zulaica, J. Domingo Toledo, and C. de Otaduy. Rev. clín. españ. **74**: 178–184, Aug. 15, 1959. (In Spanish) (Bilboa, Spain)

This is the report of a case of sarcoma of Hodgkin's type localized to the gastric antrum in a 75-year-old man. The authors discuss at length the histopathological characteristics and differential diagnosis of malignant tumors of the lymphoma group and explain their reasoning in arriving at the diagnosis in their case.

Radiographically, giant rugae were demonstrated in the gastric antrum and, during a two-month observation period, increased in size. The contour also became irregular and rigid. In early examinations, however, peristalsis was seen to pass through the area of involvement. This is supposed to be a point of differentiation from carcinoma of the stomach and is related to the differences in amount of fibrosis that develops in the two conditions.

The authors advise wide surgical resection of lesions of this type and postoperative radiotherapy. They believe it is better in patients in good condition who have had ample resection to delay irradiation until signs clinically suspicious of recurrence appear.

Nine roentgenograms; 9 photomicrographs.

DON E. MATTHIESEN, M.D.
Phoenix, Ariz.

Urticaria of the Gastric Mucosa with Massive Hemorrhage Following Oral Penicillin Anaphylaxis. S. P. Bralow and L. S. Girsh. Ann. Int. Med. **51**: 384–390, August 1959. (Temple University Medical Center, Philadelphia 40, Penna.)

The authors report the case of a 48-year-old Negro male who was admitted in shock from massive gastrointestinal bleeding and required 1,500 c.c. of blood during the first eighteen hours of hospitalization. He had taken a single oral penicillin tablet prior to his collapse, though he was known to be allergic to the drug.

A limited gastrointestinal series taken twenty-four hours after the massive bleeding revealed absence of peristaltic activity and rigidity of the gastric walls. There was an irregularity on the upper portion of the lesser curvature suggesting ulceration. The findings were thought to represent an infiltrative type of lesion. In a repeat study the following day, the stomach appeared normal, with pliable, distensible walls and no ulcer niche or deformity.

The initial gastroscopy revealed a submucosal infiltration which involved almost the entire stomach, with several hemorrhagic areas. Successive gastroscopic examinations showed rapid disappearance of the pathologic changes previously noted, and additional radiographic studies of the gastric mucosa failed to demonstrate any abnormality. After normal gastric secretion studies, the patient was discharged.

This is believed to be the first report of massive gastrointestinal bleeding caused by severe anaphylactic reaction to a single penicillin tablet. The original roentgenologic and gastroscopic findings simulated carcinoma of the stomach, and the diagnosis was made by demonstration of complete clearing of the infiltrative urticarial reaction by both these diagnostic procedures.

It is believed that when a patient known to be allergic manifests sudden severe gastrointestinal symptoms, gastric urticaria should be considered as an explanation of the bizarre radiographic and gastroscopic findings.

Two roentgenograms.

ANTONIO SIMAO, M.D.
Cleveland Metropolitan General Hospital

Correlative Study of Postgastrectomized Patients. Harvey Krieger, William E. Abbott, John S. Bradshaw, and Stanley Levey. Arch. Surg. **79**: 333–345, August 1959. (Western Reserve University, Cleveland, Ohio)

A series of patients who had been operated on for duodenal or benign gastric ulcer since 1948 were subjected to a careful investigation by the authors. The size of the series is not indicated. Evaluation included an interview which inquired into dietary habits, weight changes, and the occurrence of post-prandial symptoms. Roentgenographic studies of gastric and small intestinal transit time were carried out with upright films of the abdomen and lower chest obtained at one, twenty, forty-five, and ninety minutes after the ingestion of a barium food mixture. A group of normal volunteers

was also examined by this method. The actual daily caloric consumption was evaluated, and stool examinations were performed for determination of excess fat or nitrogen. The majority of the patients were also given 2 c.c. of 50 per cent glucose solution per kilogram of body weight in an effort to provoke symptoms. Plasma volume and peripheral blood flow were studied quite carefully.

The authors review the confusion regarding the "dumping syndrome." They attribute the wide range in the reported incidence of dumping—from 1 to 75 per cent—to a difference in definition. The term, they believe, should be limited to the rapid influx of ingested material into the small bowel (failure of the stomach or its remnant to act as a reservoir). The etiology of the symptoms occurring secondary to dumping is discussed, and the four general theories as to its mechanism are presented, along with a review of the pertinent literature.

The patients in the present series were grouped into the following categories:

1. Asymptomatic, well nourished patients, in whom roentgen examination showed normal gastric emptying and small intestinal transit times.
2. Asymptomatic, well nourished patients with rapid gastric emptying and normal or rapid small intestinal emptying.
3. Undernourished patients with or without symptoms of diarrhea or vasomotor abnormalities, with rapid gastric emptying and normal or rapid small intestinal emptying.

Patients who had small gastric stomas at the time of surgery (less than 2 cm.) fell, for the most part, into the first category, whereas those with stomas larger than 2 cm. were chiefly in categories 2 and 3. The authors do not indicate how stomal size was estimated. They do state that there may not be a correlation between the surgeon's estimate of the stomal size and its function. It is their conclusion that any anastomosis exceeding 2 cm. in internal diameter is too large; that with a small stoma the reservoir function of the stomach is preserved and signs and symptoms of dumping will be impossible.

Fourteen roentgenograms; 3 plethysmographic records; 1 graph. RICHARD H. GREENSPAN, M.D.
New Haven, Conn.

Roentgen Diagnosis of Meconium Ileus. A. D'Agostino and G. Garibaldi. Radiol. med., Milan **45:** 305–316, April 1959. (In Italian) (Istituto di Radiologia dell'Ospedale del Bambino Gesù, Rome, Italy)

Meconium ileus, a disease of the newborn which terminates in perforation and peritonitis, appears to be the consequence of a systemic condition, known as mucoviscidosis. Four cases are reported, 3 of which were diagnosed at the time of emergency surgery (1 with subsequent necropsy). All were fatal, but the fourth patient, who had a patent gastrointestinal tract (and died at the age of about twenty days), was examined both by barium meal and barium enema, which demonstrated a definite narrowing distal to the mid-transverse colon. [Could this have been an aganglionic segment? The reproductions are suggestive of megacolon.—E. R. N. G.]

The authors failed to find Neuhauser's gas bubbles in the small intestine, nor did they encounter White's sign (absence of fluid levels). They conclude that the diagnostically significant features are: (1) dilatation of bowel loops occupying the upper one-half or upper two-thirds of the abdomen; (2) microenterocolia (reduced colonic caliber, allegedly from disuse); (3) granular opacities overlying the bowel loops (inspissated meconium); (4) diffuse and/or nodular calcifications (resulting from meconium peritonitis).

Ten roentgenograms. E. R. N. GRIGG, M.D.
Cook County Hospital, Chicago

Intravenous Pro-Banthine in Diagnostic Radiology of the Gastrointestinal Tract, with Special Reference to Colonic Disease. K. Lumsden and S. C. Truelove. Brit. J. Radiol. **32:** 517–526, August 1959. (Radcliffe Infirmary, Oxford, England)

The authors' three years experience with the intravenous use of Pro-banthine has satisfied them that this drug has a profound effect upon the motility of the gastrointestinal tract and that this effect is manifest by the time the injection is completed. Side reactions are negligible. One patient suffered temporary retention of urine, which points to the importance of emptying the bladder as a precautionary measure prior to injection. There was an occasional complaint of dry mouth and blurred vision, but these disappeared in a few hours.

In the esophagus, the main effects are loss of tone and cessation of peristalsis and laxness of the cardiac sphincter. The stomach loses all evidence of peristaltic activity, together with loss of tone. Movement of the small intestine ceases, but the feathery pattern created by the valvulae conniventes remains. The colon shows dilatation and marked diminution in the haustral markings. The duration of the response varies. Return to normal may be quite sudden.

The authors find Pro-banthine quite useful in differentiating the causes of colonic block to the flow of barium. With its aid, it is possible to distinguish between spasm and organic block due to neoplasm, stricture, or an inflammatory mass. A block not relieved by intravenous Pro-banthine implies organic disease which will probably require surgery; carcinoma is the lesion most likely to be present.

In patients with block relieved by Pro-banthine, the eventual diagnosis has been either diverticulitis with spasm (but without gross pericolic thickening) or simple spasm due to functional derangement of the colon.

Fibrous stricture of the colon may be a result of inflammatory disease, especially ulcerative colitis or regional enteritis. In some cases of ulcerative colitis there appears to be a fibrous stricture when muscular spasm is the real cause of the x-ray appearance.

In cases of spastic colon, the administration of Pro-banthine permits relaxation and examination of the entire bowel without difficulty.

In ulcerative colitis the authors advise Pro-banthine only for special indications, as pain and severe diarrhea, and to distinguish spasm from organic stricture. They do not recommend its use more than once a day, since a picture of paralytic ileus is likely to be created.

In other parts of the gastrointestinal tract, such as the esophagus, the authors believe this drug is useful in distinguishing between fibrous and neoplastic strictures. By paralyzing of the esophagus and cardiac sphincter, it aids in study of varices and cardiospasm. In the stomach, hour-glass stricture can be distinguished from spasm associated with peptic ulcer. The spastic duodenal bulb may be made to hold barium, and

spasm in the precolonic region of the stomach can be distinguished from organic deformities. The capacity to relax the remainder of the duodenum is of assistance in the diagnosis of postbulbar peptic ulcer, ampullary carcinoma, annular pancreas, and pancreatic growths.

Pro-banthine does not relax the narrowed segment of a regional ileitis.

Relaxation of the sphincter of Oddi under the influence of this drug is occasionally helpful in the diagnosis of possible organic obstruction to the common duct after cholecystectomy.

The authors use 30 mg. of Pro-banthine injected intravenously over a period of one minute.

Nine cases are reported.

Eighteen roentgenograms. R. E. MILLER, M.D.
Indiana University Medical Center

Lipoma of the Colon. Report of a Case Diagnosed Roentgenographically. Richard H. Marshak and Arnold Gerson. Am. J. Digest. Dis. **4:** 628–633, August 1959. (1075 Park Ave., New York 28, N. Y.)

The authors present a case of lipoma of the ascending colon in which the roentgen findings suggested the proper diagnosis preoperatively. These findings are summarized as follows: intraluminal filling defect; sharp, smooth contours; lobulation and frequently large size; inconstant shape of filling defect; wide pedicle attachment; predilection for the right side of the colon; radiolucency.

Five roentgenograms.

RICHARD H. GREENSPAN, M.D.
New Haven, Conn.

Identification of Uncommon Liver Lobulations. John H. Feist and Elliott C. Lasser. J.A.M.A. **169:** 1859–1862, April 18, 1959. (230 Lothrop St., Pittsburgh 13, Penna.)

The authors discuss the problem of identification of masses in the right upper quadrant of the abdomen, or protruding above the diaphragm, and suggest the possibility of unusual lobulations of the liver. Four cases illustrative of this condition are presented. In 2 the variant lobule protruded through a diaphragmatic hernia, causing symptoms in 1. One patient had a Riedel's lobe in the right upper portion of the abdomen and 1 had a circumscribed lobulation of the superior liver surface without herniation through the diaphragm.

To aid in the preoperative diagnosis of these unusual lobulations, the authors suggest the utilization of a radioisotope tracer technic. In 3 of their cases they employed a liver-scanning procedure based on the affinity of the liver for the organic dye, rose bengal, to which tracer amounts of radioactive iodine (I^{131}) were chemically bound. In 2 of the cases the suspected masses were clearly identified as liver tissue. This method is a simple, specific, and innocuous diagnostic tool of value in cases of the type described, and may be used to avoid more hazardous diagnostic procedures.

Seven roentgenograms; 2 scanograms.

GEORGE A. SHIPMAN, M.D.
Staten Island, N. Y.

Stratification (Layering) of Bile in the Normal Gallbladder. Seymour A. Kaufman. Am. J. Digest. Dis. **4:** 634–637, August 1959. (Massachusetts Memorial Hospitals, Boston, Mass.)

The author discusses the mechanisms for layering of bile and contrast material in the gallbladder. The most plausible theory is that the more concentrated bile has a greater specific gravity and therefore tends to occupy the most dependent portion of the gallbladder. In the case of oral cholecystography this more concentrated "older" bile will be opacified by the contrast material given the previous day. In intravenous cholangiography, on the other hand, the denser bile will be nonopacified and the fresh bile, unconcentrated and containing the contrast material, will lie above.

Stratification is a normal physiologic phenomenon and should not be confused with stones. It may, however, be related in some way to the formation of gallstones.

Five roentgenograms.

RICHARD H. GREENSPAN, M.D.
New Haven, Conn.

The Possibility of Individualized Dosage of Contrast Medium in Oral Cholecystography. W. Graber. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 721–726, June 1959. (In German) (Lornsenplatz 2–6, Itzehoe, Germany)

In order to obtain the optimal results in demonstrating disease of the gallbladder by the oral route, the author has worked out a technic of individualizing the dose according to the weight of the patient. Using Teridax, he has obtained the best results with 0.075 gram per kilogram of body weight, that is, about 6 tablets for a patient weighing 60 kg., or 1 tablet for each 10 kg. The maximum concentration is usually reached fourteen hours after the ingestion of the medium, and that is the optimal time for filming. Aimed spot-films taken with a compression cone give the best results. The author prefers very soft rays. He uses 400 to 500 mas in a range of 45 to 62 kv.

The contraction of the gallbladder was visualized by a check-up film taken thirty minutes after the ingestion of sugar and eggs. The cystic duct could be demonstrated in 26 per cent of the cases and the common duct in 11 per cent. Larger amounts of medium in cases of poor visualization or nonvisualization do not appreciably improve the results.

This report is based on a series of 371 gallbladder examinations.

Two tables. WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

THE MUSCULOSKELETAL SYSTEM

Roentgenographic Time Lapse Studies of Living Bone. General Considerations. Howard J. Barnhard. Am. J. Roentgenol. **82:** 277–281, August 1959.

Roentgenographic Time Lapse Studies of Living Bone. A Method of Application to the Dog. Howard J. Barnhard, F. Dixon Conlin, John W. Lane, and Omer E. Bradsher. Am. J. Roentgenol. **82:** 282–289, August 1959. (Hahnemann Medical College, Philadelphia 2, Penna.)

An attempt has been made to apply the time-lapse method to the roentgenographic demonstration of changes in living bone. In the first of the two papers listed above, Barnhard discusses the general approach to the problem and the usefulness of the method.

In time-lapse studies of plant life the problem of immobilization is not encountered. In animal investigations it is a major problem. In the "ideal" system the animal would be maintained in a normal physiologic

state over a prolonged period of time while under anesthesia. The part to be studied would be held rigid and periodic roentgen exposures would be controlled by electronic timers. Such an arrangement, however, is not feasible at present. Instead, the part must be placed in exactly the same position each time it is roentgenographed. The use of plaster casts has proved unsatisfactory for this purpose, and some form of metal fixation rigidly implanted in the bone has been found preferable. This approach, however, dictates certain criteria for the selection of the subject:

1. It must be possible to apply external fixation to the bony skeleton and have it remain in position throughout the period of study.

2. The subject must be capable of co-operation sufficient to permit holding by mechanical devices. This is usually achieved by training.

3. The subject must inherently possess or be capable of the induction of the process to be studied (the rabbit, for example, will develop osteogenic sarcoma following the injection of beryllium).

The author has exposed the roentgenograms at eight, twelve, and twenty-four hour intervals, depending upon the rapidity of change. The roentgenograms are subsequently photographed on movie film.

Time-lapse sequences must be fairly short or the eye will lose its ability to perceive changes as "motion" on the screen. By trial and error, 18 frames per day have been found satisfactory in studies of osteomyelitis and fracture healing. This rate results in two-thirds of a second of projection time equalling one day of elapsed time. The time ratio is kept linear by varying the number of movie frames on which each roentgenogram is photographed.

Possible applications of the time-lapse method include studies of growth, endocrine disturbance, response of growing and mature bone to irradiation, development and response to treatment of rickets and scurvy, osteomyelitis, bone tumors, fracture healing, and bone grafts.

In the second paper, the authors outline the method employed for the study of living bone in the dog, including selection, training, and handling of the animals.

The method of external fixation is a modification of Roger Anderson pin traction and various steps in application of the fixation apparatus are listed. A pre-punched film pack is used so as to maintain accurate alignment of the roentgenograms as they are photographed on the movie film. Preparation of the film pack and the photographic apparatus are described in detail. Proposed improvements of the method are also discussed.

Ten roentgenograms; 7 photographs; 1 diagram.

RICHARD A. ELMER, M.D.
Atlanta, Ga.

Clinical Concepts in Bone Modeling. Philip Rubin and Lucy Squire. Am. J. Roentgenol. **82:** 217–228, August 1959. (Strong Memorial Hospital, Rochester 20, N. Y.)

The authors review present-day concepts of endochondral bone formation. The various congenital osteochondrodystrophies and some other diseases which cause bone changes are classified according to the site of abnormal growth and development.

Disturbances in the *epiphyseal area* are responsible for dysplasias such as achondroplasia, chondro-osteodystrophy (Morquio's disease), gargoylism, chrondroectodermal dysplasia (Ellis-van Creveld syndrome), and dysplasia epiphysalis multiplex. In this group the growth aberration takes place in the epiphyseal plate with the end result of a shortened bone.

The *metaphyseal dysplasias* include osteopetrosis (marble bones, Albers-Schönberg disease), idiopathic metaphyseal dysplasia (Pyle's disease), and chondromatosis, either of the external variety (osteochondromas) or the internal type (Ollier's disease). In these diseases the chief finding is a widened shaft due to failure of normal constriction in the juxta-epiphyseal region, while marked dwarfism is not as constant or profound a feature as it is in dysplasias of the epiphyseal area. Gaucher's disease and the appearance of dense white growth lines on the roentgenogram, as in lead and phosphorus poisoning and in healing rickets, are mentioned in this group.

Clinical examples of dysplasias involving the *diaphysis* are osteogenesis imperfecta (Lobstein's disease), trophic changes, progressive diaphyseal dysplasia (Engelmann's disease), melorheostosis, excessive periosteal reactions and Cooley's anemia. Here the abnormalities are associated with failure of normal tubulation in which over or under periosteal bone development results in a thickened or thinned cortex respectively. Actually the authors would discard the prefixes "under" and "over" as used with "tubulation," since, as used at present, these are inconsistent with the physiologic facts.

Fourteen roentgenograms; 1 photograph; 4 diagrams; 1 table.

MAX EICHWALD, M.D.
Encino, Calif.

Roentgen Evaluation of the Soft Tissues in Orthopedics. Everett L. Pirkey and James Hurt. Am. J. Roentgenol. **82:** 271–276, August 1959. (University of Louisville School of Medicine, Louisville 2, Ky.)

The authors present a series of cases which point to some of the advantages to be gained by the study of the soft tissues of the extremities as seen in roentgenograms, in addition to the usual and often quite obvious bone damage. Few of the roentgen changes are specific for a particular disease entity with the exception of lipoma, but, when correlated with the clinical findings, they may add to the overall information, permitting a more exact diagnosis both as to etiology and extent of the process.

Soft-Tissue Edema: Edema of the soft tissues is found in all traumas of the extremities. Its location and extent afford an excellent indication of the type of soft-tissue damage that has occurred. Edema is also a usual accompaniment of pyogenic infections of the bone, and is the only roentgen change seen early in such diseases. Its prompt recognition may be extremely helpful in the early institution of adequate therapy.

Soft-Tissue Atrophy: Atrophy of the soft tissues as a rule is readily apparent, both clinically and roentgenologically. It is manifest in the roentgenogram by absence of the usual muscle bundles, which when normal in size cast a shadow of water density. In an example of amyotonia congenita, described by the authors, the size of the thigh was not particularly affected, but absence of water density muscle and the presence of fat density on both sides of the fascia lata, were indicative of diminished muscular function. In other words, fatty infiltration of muscle bundles or large areas of fat density in place of the usual areas of water density indicate muscular abnormality.

Soft-Tissue Neoplasms: The classic example of the soft-tissue neoplasm that can be recognized with great accuracy is the lipoma. Almost all other tumors of the soft tissues appear as water density masses and therefore cannot be differentiated from one another on the basis of density. Their location and distribution can be determined more exactly, however, roentgenologically than by any other means short of surgery.

Twelve roentgenograms; 1 table.

RICHARD A. ELMER, M.D.
Atlanta, Ga.

Chondroectodermal Dysplasia (Ellis-van Creveld Syndrome). Report of a Case and Review of the Literature. William L. Walls, Donald H. Altman, and Oliver P. Winslow. J. Dis. Child. **98:** 242–248, August 1959. (Variety Children's Hospital, Miami, Fla.)

An additional case of the Ellis-van Creveld syndrome is reported by the authors, who review also the previous 27 authentic cases. The diagnosis can be made early after birth. There is shortening of both upper and lower extremities especially below the knees and elbows, with short stubby hands, with polydactyly and sometimes syndactyly. There is hypoplasia of the nails and sometimes hair. The teeth, if erupted, are usually dysplastic. The diagnosis is confirmed by the radiologic appearance of the skeleton. The tubular bones are short and thick. Dwarfism is due to shortening of the legs. Bilateral manual polydactylism is almost always present. The usual number of digits is six per hand, with the extra digit characteristically on the ulnar side. Polydactylism in the feet is the exception rather than the rule. Syndactylism and synmetacarpalism are prominent. The carpal bones may also be fused, especially the capitate and hamate. Delayed ossification in the primary centers and accelerated ossification of the secondary centers of the metacarpals and phalanges are usually present.

The proximal ends of the ulnae and distal ends of the radii are usually larger than normal. The distal ends of the ulnae and the proximal ends of the radii are small. There may be a discrepancy in length between the radii and ulnae leading to compensatory dislocation of the radial head. The proximal ends of the tibial shafts are widened and sharpened into low peaks with sharp medial slopes and relatively long lateral slopes. The medial slopes are capped by thin hypoplastic ossification centers in the proximal epiphyseal cartilages. This deformity is pathognomonic of Ellis-van Creveld syndrome and accounts for the classic genu valgum deformity.

Of the cases reviewed, about one-half demonstrated cardiac abnormalities. In patients dying in the neonatal period, the congenital heart lesion was a prominent feature and was felt to be the cause of death. The prognosis probably depends upon the severity of the associated cardiac malformation, if one is present.

The ectodermal dysplasia is manifested generally by defects of the teeth, nails, and hair. The teeth are retarded and imperfectly formed. The nails are small, deformed, friable or may be entirely absent. The mentality in the surviving patients is usually normal. No sex predilection exists. A simple recessive inheritance factor is thought to be present. Parental consanguinity was a feature in 9 of the 25 families studied, as compared to about 1 out of 100 families in the general population.

The authors suggest that a more appropriate and comprehensive name for this syndrome would be mesoectodermal dyplasia.

Two roentgenograms; 4 photographs; 1 table.

JOHN P. FOTOPOULOS, M.D.
Evanston, Ill.

Familial Craniometaphyseal Dysplasia. E. Hässler. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 704–713, June 1959. (In German) (Universitäts-Kinderklinik, Jena, Germany)

The condition variously known as marble bones, osteopetrosis, and Albers-Schönberg's disease is characterized by hereditary bone sclerosis, which may be of dominant or recessive type. It may be associated with anemia, which is assumed to represent an inherent factor in the disease rather than a mechanical effect upon the marrow. The x-ray findings consist in an abnormal density and an abnormal shape of the bone. While normally the shaft of a long bone shows its greatest width at the epiphyseal line and then slowly diminishes in width to produce a slender diaphysis, in Albers-Schönberg's disease the entire metaphysis may be as wide as the epiphyseal line, thus giving the long bone the shape of a club or of a bottle.

The common cause is probably a disturbance of the bone metabolism and an impairment of the osteoclasts. Inasmuch as the activity of the osteoclasts may show periodic changes in the same patient over the years, a great variety of pictures may be produced and the disease may at times resemble osteitis deformans or osteitis fibrosa. In these variable pictures three processes may be identified:

1. Extensive sclerosis without metaphyseal widening.
2. Sclerosis with metaphyseal widening and bottle-shaped diaphysis.
3. Metaphyseal widening without sclerosis.

There is some doubt as to whether this third group should be classified as Albers-Schönberg's disease, and it has accordingly been designated "familial metaphyseal dysplasia." Frequently familial metaphyseal dysplasia is associated with an enlargement and a sclerosis of the skull and the mandible, in which case the name "cranio-metaphyseal dysplasia" is suggested.

The author describes a case that has been followed from infancy to the age of twenty-two years. The sclerotic processes were initially very prominent but diminished greatly during subsequent development. The patient had a definite enlargement of the skull and a scoliosis appeared during adolescence. The scoliosis is attributed not to rickets, but rather to softening of the bone, which is quite common in this disease.

Nine roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

Osteopathia Condensans Disseminata (Osteopoikilosis); Study of a Family of 4 Generations. John C. Melnick. Am. J. Roentgenol. **82:** 229–238, August 1959. (Youngstown Hospital Association, Youngstown, Ohio)

The hereditary nature of osteopoikilosis is demonstrated in this study of four generations in a family. A total of 17 cases was found.

The author prefers the term "osteopathia condensans disseminata" to other less accurate and misleading

terms such as osteopoikilosis, osteosclerosis fragilis, osteopoecilia, osteosclerosis, Albers-Schönberg disease, and osteitis condensans generalisata.

The literature is reviewed and the roentgenographic findings are described. A chart shows in detail the distribution of the disease among the family members. Genetically this disease appears to be caused by a dominantly inherited autosomal gene.

Seventeen roentgenograms; 1 chart; 1 table.

MAX EICHWALD, M.D.
Encino, Calif.

Myelofibrosis: The General and Radiologic Findings in 25 Proved Cases. Ted F. Leigh, Charles C. Corley, Jr., Charles M. Huguley, Jr., and James V. Rogers, Jr. Am. J. Roentgenol. **82:** 183–193, August 1959. (Emory University Clinic, Atlanta 22, Ga.)

This is a report of 25 cases of myelofibrosis, an unusual disease characterized by fibrotic and sclerotic bone marrow and extramedullary hematopoiesis. The etiology is unknown. It has been postulated that polycythemia vera, chronic myelocytic leukemia, and myelofibrosis are different phases of the same myeloproliferative type of disease. Other names for the condition are agnogenic myeloid metaplasia, aleukemic myelosis, and megakaryocytic myelosis.

Clinically there are an equal number of male and female patients, most of whom are in the older age group. The onset is insidious, with weakness, fatigue, dyspnea, and weight loss. There may be abdominal pain associated with splenomegaly. There is usually a moderate to severe anemia. The red cells vary in size, shape, and nuclear content. Reticulocytes are increased. The white count is usually elevated, with a shift to the left. Bone marrow biopsy is usually necessary for a diagnosis. Physical examination reveals splenomegaly, hepatomegaly, pallor, and often purpura.

Extramedullary hematopoiesis occurs primarily in the spleen but also in the liver and lymph nodes, and to a lesser extent in the kidneys, lungs, and other organs.

Roentgenographic findings are splenomegaly, hepatomegaly, and osteosclerosis.

Osteosclerosis occurred in slightly more than half of the authors' cases. Since the sclerosis is primarily an overgrowth of the trabeculae of the spongiosa it is best seen in the flat bones of the ribs, pelvis, vertebrae, clavicle, and scapula, and to a lesser extent in the distal femoral and humeral metaphyses. There is no periosteal new bone formation.

To be differentiated are osteoblastic metastases due to Hodgkin's disease, lymphoma, or carcinoma; chronic hemolytic anemias where, however, the bone pattern is usually quite different and is well seen in the skull; Albers-Schönberg's disease (osteopetrosis).

Treatment is symptomatic. Splenectomy is usually inadvisable.

Thirteen roentgenograms; 3 photomicrographs; 6 tables.

PAUL MASSIK, M.D.
Quincy, Mass.

Joint Infections Following Steroid Therapy: Roentgen Manifestations. Roderick L. Tondreau, Philip J. Hodes, and Erwin R. Schmidt, Jr. Am. J. Roentgenol. **82:** 258–270, August 1959. (Holy Redeemer Hospital, Meadowbrook, Penna.)

A series of 17 cases in which joint infections developed following steroid therapy is presented by the authors. Sixteen of the patients had received intra-articular hydrocortisone injections over a considerable period of time, in some instances several years. The injections were given chiefly for rheumatoid and degenerative joint disease. Where information on this point was available, it was found that the onset of untoward symptoms usually took place within twenty-four to forty-eight hours following an intra-articular injection. As a rule hydrocortisone did not mask the symptoms, as has often been noted in patients receiving systemic steroids. In 2 patients, however, who received cortisone orally as well as intra-articular hydrocortisone, onset of symptoms did not take place until five and twelve days after the last injection. It is suggested that this may have been due to the masking effect of systemic therapy.

One patient received only oral steroids for a prolonged period of time, in the treatment of lupus erythematosus. Tuberculous arthritis of the hip developed after the patient had been on Meticorten daily for two and one-half years.

It is thought that in all likelihood the infections were caused by breaches of technic. In the cases in which systemic steroids were used, however, the authors believe that these compounds played a role in the initiation and spread of the infection by interfering with a normal defense mechanism of the host.

The roentgenograms of 13 patients in this group were available for review. Seven patients exhibited definite septic arthritis. In 1 patient there was demineralization, with possible bone destruction, secondary to infection. Two patients had evidence of underlying rheumatoid or degenerative joint disease but no evidence of septic arthritis. Both of these patients had clinical and bacteriologic proof of infection, but the processes were brought under control before roentgenographic changes developed.

Sixteen roentgenograms; 1 table.

RICHARD A. ELMER, M.D.
Atlanta, Ga.

The Roentgen Manifestations of Urticaria Pigmentosa (Mastocytosis). Maxwell H. Poppel, Walter F. Gruber, Robert Silber, Adrien K. Holder, and Robert O. Christman. Am. J. Roentgenol. **82:** 239–249, August 1959. (550 First Ave., New York 16, N. Y.)

Up to about ten years ago urticaria pigmentosa was thought to be a skin disease. Its systemic character is now recognized. Not only the skin but lymph nodes, spleen, liver, bone marrow, and other organs are involved. The bone changes are of particular interest to radiologists.

The clinical and pathological features of the condition are reviewed. Essentially it is a proliferative disease of tissue mast cells involving mainly the organs connected with the reticuloendothelial system. Some writers believe that it is a reticuloendothelial disease and the name mastocytosis has been suggested.

Tissue mast cell proliferation in the bone marrow may produce bone changes recognizable roentgenologically. Of 9 histologically proved cases seen by the authors, 3 had bone changes, and 1 of these is described in detail. The lesions found in the skull, spine and pelvis consisted in multiple round and oval lytic areas measuring from a few millimeters to 1.5 cm. in diameter. They were sharply demarcated, with nonsclerotic margins. Also observed were condensing bone islands measuring from 3 mm. to 2.5 cm. in diame-

ter. The authors observed the growth of one of these islands over several years.

The histologic changes cause bone resorption and bone production, which correlate with the roentgen findings of increased lucency and increased density.

Five roentgenograms; 1 photograph; 3 photomicrographs; 1 table. MAX EICHWALD, M.D. Encino, Calif.

Osteoid Osteoma: A Report on 80 Cases. Robert H. Freiberger, Bernard S. Loitman, Milton Helpern, and T. C. Thompson. Am. J. Roentgenol. **82:** 194–205, August 1959. (535 East 70th St., New York 21, N. Y.)

This is a report of 80 osteoid osteomas—28 in the femur, 19 in the tibia, 8 in the phalanges of the hand, 5 in the ulna, and 3 or fewer in other bones. The primary symptom is dull, aching, constant pain which is worse at night but relieved by small doses of aspirin. The pain may be referred to an adjacent joint. Depending on the location, there may or may not be soft-tissue swelling; usually swelling is present if the lesion is superficial. Of 57 patients with lower extremity lesions, 20 displayed a limp with limitation of joint motion. If there is sufficient disuse due to pain there may be muscle atrophy, weakness, and decreased deep tendon reflexes. Three cases in the series involved the spine, and in these there was a rigid painful scoliosis with concavity toward the affected side. There were no systemic symptoms.

Roentgenograms usually reveal a radiolucent center (nidus) surrounded by a zone of radiopacity (perifocal sclerotic bone). Pathologically the nidus appears as a dark red vascular focus surrounded by dense ivory-white bone. There is no evidence of infection.

The treatment is either surgical excision or prolonged observation. Spontaneous regression may eventually ensue.

The differential diagnosis includes chronic bone abscess, osteitis, malignant bone tumor in its early destructive stage, and a variety of benign bone lesions, such as fibrous dysplasia, enchondroma, simple and aneurysmal bone cysts, and eosinophilic granuloma.

Fifteen roentgenograms; 2 photomicrographs; 1 photograph; 3 tables. PAUL MASSIK, M.D. Quincy, Mass.

Vertebra Plana (Calvé). W. J. Weston and G. M. Goodson. J. Bone & Joint Surg. **41-B:** 477–485, August 1959. (Hutt Hospital, Lower Hutt, N. Z.)

A case of vertebra plana (Calvé) is described, and serial radiographs obtained throughout the course of the disease are reproduced. The patient was a quarter-caste Maori girl aged three years. She was first seen twelve days after the first of several attacks of severe back pain. The initial radiographs showed loss of the lumbar curve but no other abnormality. Eight days later there was collapse of the body of the fifth lumbar vertebra, with increase in the depth of the adjacent spaces. After another week, the body of the vertebra had been reduced to a thin disk. The superior and inferior end-plates appeared intact and there was further increase in the depth of the disk spaces above and below. Also, there was some loss of bone substance in the pedicles. The whole process up to this point had taken a total of twenty-seven days. Immobilization over a long period was attended by evidence of gradual healing and renewed growth of the vertebral body. Five years after the patient was first seen the body of the affected vertebra was about half normal depth. Restitution to normal shape is not to be expected.

The authors also reviewed the literature for evidence of the underlying pathologic process. In addition to osteochondritis, which was the commonest cause, others have been reported, including Hand-Schüller-Christian disease, Hodgkin's disease, osteogenesis imperfecta, hyperparathyroidism, unidentified malignant disease, eosinophilic granuloma, and injury in tetanus. The uncertainty about the pathologic process in most cases of Calvé's disease is due to the infrequency of histological study of material from the affected vertebra. In the case described by the authors, no biopsy was carried out.

Six roentgenograms; 10 diagrams.

A. R. ABLA, M.D.
Cleveland Metropolitan General Hospital

Spina Bifida Occulta With Engagement of the Fifth Lumbar Spinous Process. A Cause of Low Back Pain and Sciatica. Carlos E. de Anquin. J. Bone & Joint Surg. **41-B:** 486–490, August 1959. (Military Hospital, Cordoba, Argentina)

The author shows how low back pain can be caused in spina bifida occulta by the impingement of the spinous process of the fifth lumbar vertebra on either the stumps of the laminae of the first sacral vertebra or the fibrous band that lies between the stumps. This mechanism of pain production is more likely to occur when the increased range of extension is accentuated by a more than usually horizontal sacrum, an abnormally long fifth lumbar spinous process, or laxity of the anterior longitudinal ligament, which should control hyperextension.

Fifteen cases were seen in which the fifth lumbar spinous process was pressing on the fibrous membrane that closes the spina bifida or on the bony stumps of the defective lamina. That this is a cause of low back pain, with or without pain referred to the lower limbs, is supported by the findings at operation and the results of treatment. Eleven patients were treated by operation; in each, the spinous process of the fifth lumbar vertebra pressed against the spina bifida, either directly or through the vestigial remnant of the first sacral spinous process. In 8 cases, the fibrous membrane was adherent to the dura mater; in 1 case, the nerve roots were adherent. Excision of the fifth lumbar spinous process and the membrane across the breach of the spina bifida was an effective method of treatment. Of the 11 patients so treated, 8 had excellent results and became symptom-free; 2 had good results, with few symptoms in the lumbosacral region, and in 1 the result was only fair, with persistence of some lumbosacral pain.

Eight roentgenograms; 1 diagram; 2 tables.

A. R. ABLA, M.D.
Cleveland Metropolitan General Hospital

Hydatid Disease of the Spine. R. O. Murray and Fuad Haddad. J. Bone & Joint Surg. **41-B:** 499–506, August 1959. (R. O. M., 25 Wimpole St., London, W. 1, England)

Howorth's extensive review of the literature (J. Bone & Joint Surg. **27:** 401, 1945. Abst. in Radiology **46:** 539, 1946) and the Hydatid Registry of the Royal Australian College of Surgeons suggest the

occurrence of bone involvement in about 1 per cent and 2.4 per cent, respectively, of all cases of hydatid disease. The commonest sites of bone lesions are the pelvis, spine, and the sacrum.

Early skeletal roentgen findings consist of ill defined areas of radiolucency, without sclerotic or periosteal reaction, resembling a bunch of grapes. Later these areas become well defined and are surrounded by sclerosis. As the cysts develop, the changes due to compression become more manifest and lead to thinning of the cortex and its eventual break. At this advanced stage, the cysts and daughter cysts develop outside the bone, in the soft tissues, producing soft-tissue shadows with smooth and rounded margins. These may later calcify. When the disease affects the spine, unless secondary infection supervenes, the intervertebral disk spaces remain intact. Erosion and destruction of the laminae and pedicles are seen. There may be extensive involvement of the ribs, with expansion and thinning of the cortex.

A positive Casoni or Weinberg test can help in the differential diagnosis, but these are often falsely negative. Eosinophilia may give an indication of the disease, but is a common finding, also, in intestinal infection. A chest radiograph showing rounded cysts may afford a clue to the diagnosis.

In the 3 cases reported here, seen at the American University and Orient Hospitals of Beirut, the radiological features consisted of destructive changes in the thoracic spine, erosion of the pedicles and laminae, rib involvement with expansion, paravertebral soft-tissue shadow, cysts in the lungs, and partial and complete block of the spinal canal shown on myelographs. In each case there were cord pressure symptoms. Operative decompression relieved these totally in one instance, incompletely in another, and not at all in the third and most advanced case.

Nine roentgenograms.

FREIDOUN ESKANDARI, M.D.
Cleveland Metropolitan General Hospital

The Place of Lumbar Discography in the Elucidation of Low Back Pain With or Without Sciatica. A. I. Rhydderch. M. J. Australia **2:** 219–220, Aug. 15, 1959. (Sydney Hospital, Sydney, Australia)

With discography, disintegration of the normal disk structure can be demonstrated in cases in which the plain film or myelogram may show no abnormality. Observations on the procedure have confirmed two basic facts. With the direct transdural approach, which is employed by the author, the actual puncture of the normal disk is practically painless and only a little of the contrast medium can be introduced into the disk. The abnormal disk is far more sensitive and admits a larger amount of the contrast material. In disk derangement the exact pattern of pain can be reproduced by increasing the volume of the injection.

In practice, discography has achieved the following objects: (1) enabled a confident diagnosis of internal disk rupture to be made; (2) conversely, excluded disk abnormality at the lower lumbar levels as the cause of pain; (3) in widespread disk degeneration, obvious on plain x-ray examination, facilitated localization by reproducing the pain.

Several cases are briefly reported.

Seven roentgenograms.

ZOLTON SZALONTAY, M.D.
Mercy Hospital, Pittsburgh, Penna.

Bilateral Hereditary Micro-Epiphysial Dysplasia of the Hips. L. Elsbach. J. Bone & Joint Surg. **41-B:** 514–523, August 1959. (Insulindeweg 23, Delft, Holland)

Roentgen demonstration of a remarkably small capital femoral epiphysis, widening of the corresponding joint space, and delayed fusion of the nuclei of the upper epiphyses of the humerus and the nuclei of the carpus in an eight-year-old boy with a four-year history of pain in the knees led to a careful examination of the members of his family over four generations. Seventeen additional cases were discovered. Several of the younger members of the family showed radiographic changes similar to those in the author's patient. The elder ones had flattened femoral heads with superolateral spurs and beaking, occasional cyst formation, and osteoarthritis. No necrosis or stippling of the epiphyses, irregularity of the joint-line, abnormality of the acetabula, or involvement of the spine was noted.

The study of the family tree led to the conclusion that the disease is transmitted as a dominant; that is to say, approximately 50 per cent of the children of a diseased parent are affected and a healthy parent has no child with the disease.

One may assume that this hereditary hip disease constitutes a generalized epiphyseal growth disturbance, in which the epiphyses about the hip joints are the most seriously affected. The lesions are symmetrical, begin at the age of four at the latest, and in children consist of reduction in the depth of the upper femoral epiphyses, which show a homogeneous, coarse structure without necrosis or fragmentation. The femoral neck is shortened, but there is no coxa vara. The intelligence is normal and there are no endocrine or metabolic disturbances.

The disease differs from Perthes' disease in the absence of necrosis and fragmentation of the epiphyses, and in its bilateral character. Lack of irregularity and stippling of the epiphyses and absence of stunted growth and short fingers differentiate it from dysplasia epiphysialis multiplex. In Morquio-Brailsford's disease, there are typical enlargement and irregularity of the acetabula and also involvement of the spine. Ribbing's disease is characterized by avascular necrosis of the epiphyses and the affected members of the family are well developed in contrast to the patients with bilateral hereditary micro-epiphyseal dysplasia of the hips, who are usually small. The dwarfism and infantilism seen in cretinism do not occur.

It seems that in all the above mentioned diseases there is an underlying epiphyseal growth disturbance, which is most severe in Morquio's disease and least marked in bilateral hereditary micro-epiphyseal dysplasia of the hips, in which the wear and tear of daily life and weight-bearing cause flattening of the small and inadequate epiphyses but without necrosis or fragmentation.

Eighteen roentgenograms; 1 photograph; 1 chart; 1 table.

FREIDOUN ESKANDARI, M.D.
Cleveland Metropolitan General Hospital

The Radiographic Changes in Perthes' Disease. J. A. O'Garra. J. Bone & Joint Surg. **41-B:** 465–476, August 1959. (Royal Liverpool Children's Hospital, Liverpool, England)

Twenty-five selected cases of Perthes' disease are reported. These are divided into two groups according to the extent and location of the changes:

Group I: In this group, comprising 20 of the author's cases, the anterior half or two-thirds of the femoral head is affected. Prognosis is better and recovery more rapid than in the second group. First, the anterior segment of the head is abnormally dense; then, the dense bone is replaced by a translucent area, initially shaped like a tongue. This spreads through the whole front of the epiphysis, leaving a peripheral rim of bone. The process of apparent fragmentation and reconstruction was completed rapidly in children under eight years of age, but seemed to be much slower in older children. Generally, reconstruction was first shown as a fine strip of new bone in the periphery, which spread slowly forward and inward until the apparent defect was made good.

Group II: In 5 of the author's cases the whole epiphysis was involved, and in all of these flattening and apparent fragmentation occurred early. Reconstruction did not begin as soon as in the first group; as much as a year might elapse before any apparent change. This then took the form of a slow progressive increase in the depth of the epiphysis.

The author emphasizes the importance of lateral views for detecting early changes and following the progress of the condition and the stage of reconstruction.

Forty-four roentgenograms; 1 table.

A. R. ABLA, M.D.
Cleveland Metropolitan General Hospital

Massive Osteolysis of Pelvis Due to Osseous Metastasis of Thyroid Carcinoma. K. S. Bose and B. Choudhuri. J. Indian M. A. **33:** 97–98, Aug. 1, 1959. (Medical College Hospitals, Calcutta, India)

A 40-year-old man was hospitalized for swelling of the legs, hemoptysis, severe emaciation, and weakness. Prominent veins were present over the lower half of the abdomen and in the left groin. Tenderness was elicited by pressure over the left hip and pelvis. A nodular swelling of the thyroid was said to have been present for at least twenty-two years and was asymptomatic. Chest films showed thyroid calcification, deviation of the trachea to the left, and left pleural effusion.

Roentgen examination of the pelvis demonstrated widespread destruction of both ilii and ischii, and of the sacrum, with extension across the joint lines. Punched out bone lesions were noted in the neck of the femur. Needle biopsy yielded blood without malignant cells. The needle "went through as if into butter without any bony resistance." On the basis of the clinical findings a presumptive diagnosis of so-called "massive osteolysis" was made. Angiosarcoma was suggested by the radiologist.

The patient deteriorated rapidly. Important points of the autopsy report included diffuse enlargement of the thyroid, diagnosed histologically as follicular adenocarcinoma. A massive fleshy infiltrative tumor occupied almost the entire bony pelvis and gluteal regions, with the same histologic features as the thyroid tumor. Metastases were also found in the femurs, ribs, spine, and skull.

This case demonstrates the fact that metastatic tumor, particularly if of a very vascular type, may simulate the clinical entity massive osteolysis of bone.

The one small roentgenogram is not helpful. One photograph and three photomicrographs are also included.

JAMES W. BARBER, M.D.
Cheyenne, Wyo.

A Rare Form of Acro-Osteolysis. Maria Fogel, Dezsö Vajda, and László Urai. Fortschr. a. d. Geb. d. Röntgenstrahlen **91:** 243–248, August 1959. (In German) (III. Chirurgische Universitätsklinik, Budapest, Hungary)

The authors describe two cases of band-like osteolysis of the diaphyses of the terminal phalanges of the hand. The first case was one of Raynaud's disease. Roentgenograms showed osteolysis of the diaphysis of the terminal phalanges and small cystic areas in the carpal and metacarpal bones; the joint space was normal. Arteriography revealed marked obliteration of the lumen of the vessels, which terminated at the middle phalanges. The interosseous arteries failed to fill. Venous filling was also markedly decreased. The cold-agglutinin test was positive. On re-examination, two and a half years later, roentgenograms showed almost complete reconstruction of the terminal phalanges, only the unguinal tufts being mildly sclerotic. The arteriogram was normal, and venous filling was within normal limits. The small cystic changes of the carpal and metacarpal bones were unchanged. The cold-agglutinin test was now negative.

The second patient had scleroderma and also exhibited band-like osteolysis of all distal phalanges. Arteriography was not performed in this case.

The authors believe that the osteolysis is secondary to the vascular and circulatory disturbances, which he feels must exist for some time before the occurrence of bone changes. They attribute the vascular and bone changes in his first patient to the obstructive mechanism of the cold agglutinins. This patient gave a six-month history of exposure to cold.

Osteolysis may also be associated with other diseases, as osteomalacia, primary and secondary hyperparathyroidism, and gastrointestinal disorders, and as a familial condition.

Seven roentgenograms.

ILONA D. SCOTT, M.D.
Lewisburg, W. Va.

Post-Traumatic Ossification of Accessory Bones. W. Brauer. Fortschr. a. d. Geb. d. Röntgenstrahlen **90:** 713–716, June 1959. (In German) (Chirurgische Universitätsklinik der Charité, Berlin, Germany)

In wrist injuries a fractured styloid process of the ulna usually fails to unite with that bone and remains as an isolated fragment. The author has observed that in wrist fractures in children with a still cartilaginous styloid process, the latter is rapidly ossified so that by the time the fracture is healed, the x-ray film shows the same isolated fragment as in adults. He believes that many little ossicles diagnosed as accessory bones (os triangular) probably represent the styloid process of a previous fracture.

Two cases are reported.

Eleven roentgenograms.

WILLIAM A. MARSHALL, M.D.
Chicago, Ill.

GYNECOLOGY AND OBSTETRICS

Double-Contrast Method in Hysterography with Propyliodon. J. Erbslöh. Fortschr. a. d. Geb. d. Röntgenstrahlen **91:** 249–252, August 1959. (In German) (Kreiskrankenhaus, Bad Oldesloe, Germany)

Deák and his associates (Fortschr. a. d. Geb. d. Röntgenstrahlen **88:** 422, 1958. Abst. in Radiology

72: 306, 1959) showed that it is possible to demonstrate changes in the uterine cavity and its mucosal lining by injection of a water-soluble contrast medium and follow-up air insufflation. The previous experiments *in vivo* were somewhat unsatisfactory due to uneven adherence of the contrast material to the mucosa. The reason probably lay in the physical-chemical properties of the medium.

The author has found what he considers an ideal contrast medium in Propyliodon (Cilag), which has previously been used for bronchography. In various experiments this has been proved not to cause peritoneal irritation. Experience showed that its adherence to the mucosa improves with the viscosity. Air insufflation following introduction of the medium results in improved visualization of fine detail, analogous to the double-contrast studies of the colon.

Two cases are illustrated with roentgenograms.

ILONA D. SCOTT, M.D.
Lewisburg, W. Va.

Chondrodystrophy (Achondroplasia) of the Foetus in Obstetrics. Vishnu Sarma. Brit. J. Clin. Pract. 13: 409–414, June 1959. (Government Women and Children's Hospital, Egmore, Madras, S. India)

Achondroplasia may be readily recognized at birth: The trunk of the infant is of normal length; the head is slightly enlarged; the frontal bones are prominent and the glabella is depressed; the lower jaw tends to project; the arms and legs are unusually short but broad and covered by thick folds of skin, muscle, and fat so that the extremities are maintained in a characteristically extended position. The condition appears to be more common in females. Four of the series of 14 cases reported here were in males.

In the author's experience the cause of serious obstetrical trouble has invariably been the large fetal head.

Indications for roentgenography are the presence of polyhydramnios or a suspicion of cephalopelvic disproportion. The striking features in prenatal radiographs are the extremely short extremities in relation to the length of the trunk. Other conditions to be looked for include a large head with normal calcification, the depressed glabella with a prominence of the frontal region, the demonstration in exceptionally good films of bony protuberances in the region of the foramen magnum, a lumbar curve, and abnormal shortness of the bony portion of the ribs. One case was diagnosed correctly antenatally despite poor contrast in the films due to excessive polyhydramnios.

Three cases are presented in detail.

Two roentgenograms; 8 photographs; 1 table.

THE GENITOURINARY SYSTEM

Localization of the Kidney for Renal Biopsy. Charles A. Nugent and William Stowell. J. Urol. **82:** 193–196, August 1959. (VA Hospital, Salt Lake City, Utah)

The authors describe their method for localizing the kidney for renal biopsy. The patient is prepared for intravenous urography and after the injection of the contrast medium is placed in the prone position. The biopsy site as determined from previous films is marked on the skin by a lead marker. A Balsa block (11 × 7 × 6 cm. for the average adult) is used for compression, being placed under the right side of the abdomen so that it does not push directly against the costal margin or iliac crest. After this is done, the cone is centered over the estimated site on the skin and elevated to the maximal height. This is to reduce the magnification as much as possible. The authors employed 134 cm. distance.

A grid is prepared from a 13 × 13 cm. cardboard sheet. On this cardboard two sets of 12 parallel lines 1 cm. apart and 1 cm. from the edges are drawn. At the crossings of these lines pieces of lead, 1 × 1 × 1 millimeter, are glued. For practical purposes, and to avoid scatter, the markers may be confined to the usable portion, with none in the six left rows. The grid is placed on the patient's back parallel to the table, with the left lead markers lying over the spinous processes. Two corners of the grid are marked on the skin by scratches with a knife blade, to give a reference for later replacement in the same position.

Seven minutes after the injection of the contrast medium an 8 × 10-inch film is obtained with the patient holding his breath in resting position. The technic used is the standard technic for intravenous urography, with modifications to compensate for the change in distance and the decrease in patient thickness because of the block under the abdomen.

The ideal point for the biopsy is selected on the spot film and is related to the grid by counting the rows of markers from the left and bottom margins. The grid now is replaced in the same position as before, the appropriate lead marker is found, and scratches are made at the selected point.

After preparation of the skin and the injection of a local anesthetic agent a small incision is made about 3 cm. below the finally selected point and on the same sagittal plane. The needle is introduced through this incision at a relative angle to the skin of the back, less than 90° but more than 45°. The biopsy is concluded as described by Kark and his associates (Arch. Int. Med. **101:** 439, 1958) except that this is done with the patient holding his breath and in resting position instead of in full inspiration.

Following the description of the method, the article enters into a discussion of the superiority of such a technic versus simple measurements, on the intravenous urogram, of the distance from the point of biopsy to the spine and to iliac crest. In the latter method the kidney changes in position when the block for compression of the abdomen is placed, and this change varies from patient to patient. A second disadvantage is the magnification by geometrical factors on the film. The film measurement will invariably be greater than the actual distance.

In 26 cases in which biopsy was done following the described technic, kidney tissue was obtained in all and in only one was of inadequate amount (less than 5 glomeruli).

Two figures.

ALVARO F. ECHEVERRI, M.D.
University of Pennsylvania

Milk of Calcium Renal Stone. Robert D. Howell. J. Urol. **82:** 197–199, August 1959. (1802 N. Illinois St., Indianapolis 2, Ind.)

This is a short case report of a middle-aged woman with recurrent episodes of left flank pain and pyuria. The preoperative roentgen diagnosis was a left renal calculus, but at operation the surgeon was unable to locate the stone. Postoperative roentgenograms, in the erect and decubitus positions, revealed an intrarenal

cyst containing a suspension of calcium particles with a fluid level similar to that seen in milk-of-calcium bile in the gallbladder.

It is suggested that misinterpretation of a pyelogenic cyst containing calcium particles as a solitary renal calculus may be avoided if a decubitus film is obtained.

Eight roentgenograms.

ROBERT E. CAMPBELL, M.D.
University of Pennsylvania

Ectopic Ureteral Orifice. A Report Based on Seventeen Cases. Aurelio C. Uson and J. Timothy Donovan. J. Dis. Child. **98:** 153–161, August 1959. (620 W. 168th St., New York 32, N. Y.)

In a series of 17 patients with ectopic ureteral orifices, only 2 were males, and in both of these the diagnosis was made at autopsy, in one case following death from carcinoma of the anomalous renal pelvis and in the other after renal failure as a result of malformation. These patients were aged forty-one and twenty-two years, respectively. Of the 15 cases in females only 1 was not diagnosed before adult life. This was in a woman of twenty-three years complaining of urinary incontinence, in whom an ectopic ureteral orifice was discovered in the vagina following hymenectomy. The other female patients ranged in age from three weeks to twelve years.

Pyuria, incontinence, and fever were the symptoms most frequently reported, but the 2 males and 7 of the female patients did not complain of incontinence. In 9 patients there was slight pyuria and in 4 of these there was a leukocytosis associated with fever and acute pyelonephritis.

Urethral and vaginal examinations in the 15 female patients visualized the ectopic orifice in 7 patients. In 1 case a urethrogram was successful in showing the ectopic ureter which was not previously located by urethroscopy.

The urethra was the site of the ectopic orifice in 9 patients, the vagina in 6, the rectum in 1, and the seminal vesicles in another. Ureteral ectopia is frequently associated with ipsilateral or bilateral duplication anomalies, and the ectopic ureteral orifice is always the one to drain the upper half of the involved kidney. The single case of ectopic ureteral orifice in the rectum was not associated with upper urinary tract duplication but with a partial duplication of the sigmoid colon and a rectovaginal fistula.

In reviewing the literature the authors find that this anomaly occurs predominantly in the female. Both ureters are equally involved. In males the site of the ectopic orifice is usually in the posterior urethra, with a lesser rate of occurrence in the seminal vesicles, the prostatic utricle, ejaculatory ducts, and the vas deferens. In females the most common site is in the vaginal vestibule, followed by the urethra, the vagina, the cervix, and the uterine cavity in that order.

Roentgen means of diagnosis include a plain film of the abdomen, intravenous urography, and retrograde pyelography of the anomalous tract. The diagnosis of an ectopic ureteral opening into the seminal vesicle may be made if there is evidence of a soft mass on top of a seminal vesicle associated with cystic swelling in the bladder base, along with absence of the normal orifice.

Ureteral ectopia, ureterocele, stenosis of the ureteral ostium, some types of congenital bladder neck obstruction, and complete and incomplete duplications of the upper urinary tracts are the end-results of deviation from normal embryogenesis of the mesonephric duct and its derivatives. An account of the embryology is given in great detail.

Two roentgenograms; 2 diagrams; 7 tables.

JOHN P. FOTOPOULOS, M.D.
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MISCELLANEOUS

Radiological Observations in Tropical Splenomegaly. S. P. Basu. J. Indian M. A. **33:** 121–124, Aug. 16, 1959. (School of Tropical Medicine, Calcutta, India)

It is now recognized that chronic massive enlargement of the spleen of unknown etiology, commonly designated as tropical splenomegaly, includes for the most part such conditions as postmalarial splenomegaly and intrahepatic and extrahepatic portal obstructions. The present report includes the results of radiological investigations carried out in a series of splenomegalic patients admitted into the Carmichael Hospital for Tropical Diseases, Calcutta, in 1953–1958.

Splenoportography, performed by the percutaneous method in 59 cases, revealed the degree of patency of the splenoportal veins and their tributaries within the liver substance as well as of any collaterals and helped differentiate between extra- and intrahepatic portal obstruction. Untoward reactions following the procedure are described, but if it is used with discrimination, the author believes the advantages outweigh the risk.

Esophageal varices were found in 21 of 60 patients examined by barium-swallow. No varix was demonstrated roentgenographically in 6 with a history of hemorrhage.

A full barium-meal study was made in 15 patients, in 1 of whom a varicose condition of the stomach, in addition to an esophageal varix, was observed. In all 15 there was dextrodeviation of the stomach, which was pushed medially by the enlarged spleen; the left half of the colon was pushed to the right.

Intravenous pyelography was performed in 10 cases, demonstrating ptosis and apparent enlargement of the left kidney and also failure of concentration of the contrast agent and clubbing of the calyces. After splenectomy, re-examination showed an ascent of the left kidney and restoration of function.

Roentgenography of the gallbladder in 10 cases disclosed evidence of biliary calculi in 3. Oral cholecystography in 5 cases revealed poor concentration of the medium.

In the 4 patients with skeletal studies, coarse bony trabeculations in the flat bones and osteoporosis in the small bones of the hand were found.

When superficial abdominal veins were prominent, attempts were made to visualize the collateral circulation. Injection of the medium into the superior epigastric vein did not yield much information whereas injection *via* the inferior epigastric vein sometimes resulted in visualization of the iliac vein of the affected side and its communication with the vein of the other side and a portion of the inferior vena cava. The epigastric vein was dilated and tortuous, suggesting that it was carrying an additional volume of blood.

Six cases are reported: 1 each of intrahepatic obstruction, Laennec's cirrhosis, postnecrotic cirrhosis, postmalarial splenomegaly, extrahepatic obstruction, and 1 showing the presence of the accessory portal system of Sappey.

TECHNIC; CONTRAST MEDIA

Quality and Choice of Potter Bucky Grids. I. A New Method for the Unambiguous Determination of the Quality of a Grid. II. Application of the Criterion of Quality to Various Types of Grids. III. The Choice of a Bucky Grid. J. G. Bonenkamp and W. Hondius Boldingh. Acta radiol. **51:** 479–489, June 1959; **52:** 149–157, August 1959; **52:** 241–253, September 1959. (X-Ray Laboratory of Philips' Gloeilampenfabrieken, Eindhoven, the Netherlands)

A new criterion of quality of Potter Bucky grids is suggested: Of two grids the better one gives the greater contrast at the same density, tube load, and exposure time irrespective of the required voltage. The contrast is plotted on a graph as a function of the exposure time with the voltage as a parameter, at constant density and tube load.

The method by which this quality graph is obtained is explained in Part I and several graphs are reproduced. The grid lines never intersect on the graph, meaning that, as far as contrast-improving effects are concerned, the grid with highest plot on the graph is preferable throughout the voltage range.

In Part II, the results of measurements without a grid and of those relating to 13 grids are discussed. The measurements were performed in water phantoms of 10, 20, and 30 cm., the contrast objects being 1 cm. air and 2 mm. Al. The voltage was varied between 50 and 200 kv, the added filter on the tube being 0.5 mm. Al + 0.05 mm. Cu. The exposure times were based on D [density] = 1.0 at a tube load of 4 kw, while the contrast obtained is related to γ (film gradation) = 2. In order to register the differences as clearly as possible, a wide beam (36 mm. diameter at a film-focus distance of 90 cm.) was used in all the measurements.

Grids with the highest lead content gave the greatest improvement in contrast and that content was therefore considered as a measure of the contrast-improving effect but only if the lead was applied in an effective manner, with a well chosen relationship between the height and thickness of the lamellae. This latter requirement is readily recognized if it is borne in mind that a given lead content in the form of a lead plate would provide a poor grid.

Grids with aluminum interspacing and cross grids did not produce any special improvement in contrast as compared with other grids with a corresponding lead content.

In studies on the influence of phantom thickness and contrast objects, with one exception of academic interest only, the heaviest grids yielded the greatest improvement in contrast. This conclusion obtains, then, not only independently of the voltage (50 to 200 kv), but also of phantom thickness (10 to 30 cm. of water) and contrast object (aluminum or air).

In view of the increasing interest in the dose received in radiography, measurements were carried out on all three water phantoms in the whole range of 50 to 200 kv, with 0.5 mm. Al + 0.05 mm. Cu filter, to ascertain what free-air dose is applied at a distance of 50 cm. to obtain the density 1.0 in the film when the various grids are used, and without grid. In the case of a 20-cm. phantom, filters of 1 mm. Al and 0.5 mm. Al + 0.2 mm. Cu were also used. For the sake of simplicity, neither the volume dose nor the increase of the dose at the surface of the phantom due to back-scatter was taken into account.

When a heavier grid is chosen in order to obtain better contrast, at a given exposure time, not only must the voltage be raised (*e.g.*, from 75 to 110 kv) but also a higher dose (2,500 instead of 1,400 mr) is applied. Also, with the same heavy grid and at the same dose, a shorter exposure time is obtained (0.8 instead of 1.6 sec.) when the voltage is still further raised, up to 125 kv, and one is satisfied with a slightly smaller gain in contrast.

Similar measurements were made with thinner (1 mm. Al) and thicker (0.5 mm. Al + 0.2 mm. Cu) filters to study their influence on exposure time and dose. In the case of roentgenograms of a given object, for which the voltage is so chosen that D = 1.0 is obtained with a given dose, almost the same contrast is achieved with different filters. A thinner filter then calls for a higher voltage and a shorter exposure time. The well known rules for the use of filters in diagnostic radiology (heavier filters for higher voltages) achieve a decrease in dose with a thicker filter at unaltered voltage, at the expense of loss of contrast and longer exposure time.

That heaviest grids yield the best contrast applies (1) in the case of lung radiography and (2) with the use of heavy contrast media such as iodine and barium where the loss of contrast due to high tension is often less important than the gain in exposure time. While it should not be forgotten that the blurring due to intensifying screens may be greater at high than at low tensions, there is a gain in visibility due to reduced blurring caused by movement and improvement in contrast.

Nineteen diagrams; 2 tables.

In Part III, an analysis of the fact that the lead content is the main criterion of grid quality is made and rules are derived for a suitable choice of grid for a given field of application. The indication of the lead content (mg./sq. cm.) on each grid is strongly recommended. It is possible to characterize the grid efficiently by means of the following practical and important data: nominal focus distance; number of lamellae per cm.; height/distance ratio (in the case of cross-grids 2 × ...); lead content, mg./sq. cm.

Nine diagrams.

Is a Fluoroscope Useful to the General Practitioner? Israel E. Kirsh. J.A.M.A. **170:** 1141–1142, July 4, 1959. (VA Hospital, Hines, Ill.)

The author presents strong arguments for the abandonment of simple fluoroscopy, *i.e.*, apart from radiography, questioning both its safety and its usefulness.

Surveys have shown wide variations in radiation output of fluoroscopes, up to 118 r per minute. On one of the author's machines, a two-minute chest fluoroscopy would give the patient at least 5.6 r, compared with 0.031 r for a postero-anterior film. A busy practitioner may fail to dark-adapt adequately, with the result that he suffers the handicap of less than optimal vision or he tries to increase the illumination of the screen by raising the intensity of the x-ray beam, which would result in increased radiation to the patient. In contrast, a roentgenologist schedules his work so that he is dark adapted, and supplements his findings with spot films and ordinary radiographs. This frequent comparison improves his fluoroscopic ability and impresses him with the size and importance of lesions shown on films which can be missed fluoroscopically. A humbling and educational experience of this kind is unavailable to the physician who depends on his fluoro-

scope and who does not check his findings, whether positive or negative, by films.

Fluoroscopy is useful as a supplement to radiography, preferably by a roentgenologist. The use of the fluoroscope alone by the practitioner is likely to give relatively little diagnostic information for the radiation involved, and may create a false sense of security.

GARTH R. DREWRY, M.D.
Tampa, Fla.

The Effects of Barium Sulfate on the Lungs. A Clinical and Experimental Study. James K. V. Willson, Paul S. Rubin, and T. M. McGee. Am. J. Roentgenol. **82:** 84–94, July 1959. (Johns Hopkins University School of Medicine, Baltimore 5, Md.)

Sixteen cases of aspiration of barium sulfate, collected from the files of the Johns Hopkins Hospital, are summarized, and experimental observations on intratracheal instillation of barium in 20 dogs are recorded. The previous literature pertaining to the effects of aspiration and instillation of barium into the lungs is also reviewed.

Both the clinical and experimental observations indicate that barium sulfate acts as a nontoxic, inert foreign body within the lungs. Histologic examinations in the animal experiments showed only a mild foreign-body reaction and no evidence of fibrosis. The respiratory tract appeared to be very efficient in removing barium sulfate from the bronchial tree.

In the experimental animals barium sulfate sometimes produced foci of atelectasis or emphysema by mechanically plugging the bronchi. It is emphasized, however, that these conditions were "spotty," affecting only a small fraction of total lung volume. Pathologically it was observed that the cellular reaction consisted principally of mild bronchial and peribronchial inflammatory changes with phagocytes penetrating into the mass of barium sulfate within the bronchial lumen.

The practical points gained by this study appear to be that no reaction need be anticipated and no specific therapy is indicated following aspiration of barium sulfate. There is no contraindication to bronchography with barium sulfate, though the instillation of a large amount into a small volume of lung may be undesirable. Further study of the mechanical effects of barium sulfate is necessary.

Nine roentgenograms; 5 photomicrographs; 3 tables.

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Nature of Adverse Reactions to Radiopaque Agents. Preliminary Report. Sidney S. Sobin, Wallace G. Frasher, George Jacobson, and Frank A. VanEeckhoven. J.A.M.A. **170:** 1546–1547, July 25, 1959. (Los Angeles County Hospital, Los Angeles, Calif.)

The authors studied the effect of intravenous injection of Hypaque and Miokon on the small blood vessels at the corneoscleral junction in man and rabbits. Arterioles and venules 75 microns in diameter, or larger, could be easily observed by means of a binocular microscope.

In 20 of 24 men studied during intravenous urography, characteristic changes occurred in the corneoscleral vessels, varying only in degree. One to two minutes after the conclusion of the injection there was marked slowing of the microcirculation, and the fine granular appearance of the erythrocyte column was quickly replaced by a much coarser granularity with alternating red blood cell masses and clear plasma zones. Irregular arterial and venous constriction were noted, at times with almost complete pinching off of the red blood cell column and formation of slowly moving sausage-like masses. The overall vascularity of the field was decreased. The effect was maximal at four to six minutes after injection, and in most instances the appearance had returned to normal in twenty minutes.

Injection of the same substances or of Urokon into rabbits caused similar changes but with more rapid onset and greater intensity.

The cause of the blood vessel changes and the red cell aggregates is not known.

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RADIOTHERAPY

Malignant Disease of the Antrum. V. M. Dalley. Brit. J. Radiol. **32:** 378–385, June 1959. (Royal Marsden Hospital, London, S. W. 3, England)

The author reviews 172 cases of cancer of the maxillary antrum and 43 of cancer of the ethmoid. A classification was developed, based on the anatomy of the maxilla, dividing the cases according to the process (zygomatic, palatine, frontal, or alveolar) most affected by the neoplasm.

It was felt that the basis of treatment should be a combination of radiotherapy and surgery. Radiotherapy was given first in the form of external irradiation for two reasons: (1) As most of the tumors are extensive, it is easier to treat the entire mass by radiotherapy than to attempt surgical removal. (2) It is an advantage to treat by radiotherapy when the blood supply is intact, as the response is usually better. Preliminary irradiation reduces the scope and extent of any surgical procedure subsequently necessary, particularly in respect to the orbit.

Exceptions to the routine are: the very early case, where the tumor appears to be completely removable by surgery, in which event postoperative radiotherapy is employed, and the zygomatic group of cases, where the presence of cancer and sepsis in the dense bone of the zygomatic malar arch both reduces tumor sensitivity and increases the risk of radionecrosis, with the consequence that the tumor often increases in size under treatment.

Routine pre-treatment procedures are: establishment of the diagnosis by means of a biopsy and a Caldwell-Luc operation, if necessary, and removal of septic teeth.

Radiotherapy is given by external x-rays, the treated area including the maxillary and ethmoidal sinuses and the nasal fossa and orbit on the diseased side. Most of the patients are treated at 250 kv, through three fields on a cast, so arranged as to spare the whole of the orbit on the normal side; on the diseased side only corneal protection is employed. The dosage to the tumor is usually 4,500 to 5,000 r in five to six weeks.

The development of radiation cataract is one of the

most serious complications of treatment. Bilateral cataracts occurred in 6 cases in this series, usually following the use of a technic which ignored the dose given to the lens through the posterior or lateral fields. Unilateral cataracts have so far been considered a justifiable sequel of treatment and appeared in 10 cases. Experience at the Fondation Curie seems to show that it is possible to give a dose of 2,500 r to the unprotected orbit, without signs of cataract five years later. Individual susceptibility varies.

The five-year survival figures are based on 87 cases of antral and 25 cases of ethmoid cancer. They are 30 per cent and 20 per cent, respectively. The three-year figures show 34 per cent survivals for 106 cancers of the antrum and 34 per cent for 32 ethmoid cases.

Nineteen figures; 6 tables.

CHARLES H. HELMEN, M.D.
Indiana University Medical Center

X-Ray Therapy of Sinusitis. Gerhard Gabriel and Enrique Schwarz. Virginia M. Monthly **86:** 472–475, August 1959. (Johnston Memorial Clinic, Abingdon, Va.)

Four hundred and sixty-six cases of sinusitis were treated with roentgen irradiation in a period of eight years in the Johnston Memorial Clinic, Abingdon, Va. Nine patients were under twenty years of age and 17 were under forty, the youngest being seven and the oldest seventy-eight. Less than half were males. In a large number of the cases symptoms had been present for only one year, but for the entire series their duration ranged from two weeks to thirty years. There were positive radiographic signs of sinus disease in all the treated patients.

Treatment factors were 140 kv, 15 ma, 31 cm. distance, 0.25 mm. Cu and 1.0 mm. Al (h.v.l. 0.55). Four treatments of 100 to 125 r each (in air) were given in two weeks directed to the sinuses anteriorly. All cavities were irradiated at each treatment, with lead shields covering the eyes, eyebrows, upper lip and mouth, upper portion of the forehead, and both sides of the face. Where hypertrophied lymphoid tissue was found in the nasopharynx, the patient received additional therapy through two lateral pharyngeal ports the third week. Patients having symptoms of recent onset were given no more than 100 r per treatment. No immediate or late reactions were noted.

Post-therapy data were available for 306 patients. There was prompt symptomatic relief in 186. Thirty-two of these had received therapy additional to the irradiation, leaving 154 (50 per cent of those followed) who obtained relief from x-rays alone. Irradiation was considered a definite failure in 44 cases (15 per cent), probably because of allergic origin of the sinusitis.

Careful selection of patients is important. Those with extensive polypoid formation are best treated by other methods, and proper drainage is needed for beneficial results when acute sinusitis is present.

Clinical and Pathological Considerations on Tumors of the Salivary Glands and Homologous Mucosal Glands. P. Desaive, A. de Scoville, and G. Gilson. J. belge de radiol. **42:** 331–504, 1959. (In French) (Université de Liège, Belgium)

During the last thirty-two years, 200 patients with 201 neoplasms of the salivary glands were treated at the Anticancer Center of the University of Liège. This number included 11 benign growths (adenomas and others), 6 lymphosarcomas, 114 so-called mixed tumors (83 localized and 31 infiltrating), and 70 primary carcinomas. Lymph-node involvement (20 cases), as well as distant metastasis (14 cases), was relatively rare. A tendency to local recurrence is highly characteristic of the evolution of salivary gland tumors.

Four patients received no treatment at all because of their desperate state. Forty-four were treated by operation alone (22 radically), with 29 survivals and 8 deaths from other causes than salivary gland cancer (81.72 per cent good results from the salivary point of view). One hundred and thirty-four were operated upon (54 radically) and received postoperative irradiation, with 89 survivals and 17 deaths from other causes (66.4 per cent good results). Nineteen received irradiation only (17) or other treatments (2), with 7 survivals, 6 deaths from intercurrent disease, and 1 from cancer of the liver (78.7 per cent good results).

The authors found that local recurrences are fewer (10 per cent) when surgery is followed by irradiation than after surgery alone (59 per cent). They conclude that "early and extensive treatment, based on a good radiosurgical association, could give far better results, taking into account that most of the salivary gland tumors show a relatively slight tendency to metastasis."

Eight roentgenograms; 16 photomicrographs; 26 photographs; 30 tables. RENÉ HOURI, M.D.
New York, N. Y.

Breast Carcinoma: Roentgen Therapy Alone. F. Baclesse. J. de radiol. **40:** 444–446, August-September 1959. (In French) (Paris, France)

The possibility of delayed relapses occurring after twenty, thirty, and forty years or more, makes deceptive the pretension to "cure" of breast carcinoma in the actual meaning of the word. It indicates only a stabilization, sometimes prolonged, that has the same value as a clinically apparent cure. With this in mind, roentgen therapy alone has two aims: (1) long-standing clinical disappearance of both tumor and involved lymph nodes; (2) determination of the frequency of hematologic metastasis.

Of 310 cases of breast carcinoma (none Stage I) treated by radiotherapy alone (200 kv), 100 (32.2 per cent) were clinically stabilized after more than five years, while 25 (15 per cent) of 163 patients were alive with apparent clinical stabilization after ten years. As to hematologic metastasis, it is at present impossible to say if this occurs more frequently following radiotherapy than surgery because the surgical material includes a great number of Stage I cases that are systematically eliminated in the author's series.

Failure in breast cancer is said to be due to hematologic metastasis more than to a local or regional relapse. Metastases appear to increase with lymph-node invasion to a greater extent than with progression of the primary tumor.

Six tables. RENÉ HOURI, M.D.
New York, N. Y.

Preoperative Roentgen Therapy for Cancer of the Rectum. M. W. Stearns, Jr., Michael R. Deddish, and Stuart H. Q. Quan. Surg., Gynec. & Obst. **109:** 225–229, August 1959. (Memorial Center for Cancer and Allied Diseases, New York, N. Y.)

The authors present statistics on 1,786 patients with

primary adenocarcinoma of the rectum or rectosigmoid seen at Memorial Center (New York) between 1939 and 1951; 1,276 were subjected to celiotomy and these were divided into two groups: (1) those who received preoperative therapy numbering 727, and (2) those who did not, 549. In the first group, the resectability rate was 69 per cent, compared with 86 per cent in the second group. The authors feel, however, that this difference is largely due to selection, since most of the far advanced cases were given x-ray therapy.

The overall five-year survival rate for the entire series was 28.5 per cent. For the 1,276 operated upon, the survival figure was 37.4 per cent; for the 971 in whom resection was performed, 49 per cent. In those patients subjected to celiotomy without preoperative irradiation the five-year survival rate was 41 per cent; in the irradiated group it was 35 per cent. When resection was accomplished, the five-year survival rate was 47.5 per cent if no irradiation had been given preoperatively and 51 per cent if it had.

Age, sex, and grade of the tumor did not appear to bear any relation to possible selection of patients for preoperative x-ray therapy. The patients were grouped on these bases and none of these factors seemed to play any part in the difference in the survival rates between those who received irradiation and those who did not.

The patients were also divided on the basis of Dukes' classification of the dissected specimen. Preoperative x-ray therapy did not appear to influence the survival rate in patients free of lymph-node metastasis. In the group with node involvement, however, there was a significant increase in survival rate with irradiation: 37 per cent as compared to 23 per cent among those not subjected to preoperative irradiation.

The incidence of liver metastasis at operation was significantly higher for those who had preoperative irradiation (18.5 per cent) than in those who had not (11.2 per cent). Again the authors felt that this was largely a matter of selection of patients, though admitting that there might be some postponement of resection following x-ray therapy. Delay greater than one month was believed likely to increase the incidence of liver metastasis.

On the basis of this study, the authors conclude that preoperative irradiation for adenocarcinoma of the rectum is indicated. They feel that the significant increase of survival rate in those patients with lymph-node metastases is sufficient to warrant this conclusion.

Seven tables.

WALLACE T. MILLER, M.D.
University of Pennsylvania

On the Influence of Magnitude and Distribution of Radiation Dose Upon the Cure Rate of Carcinoma, with Special Reference to Cervical Cancer Patients Treated in 1947 and from 1950 to 1952 at the University of Erlangen Gynecological Clinic. Jörg-Peter Brasch. Strahlentherapie **107:** 197–233, October 1958. (In German) (Universitäts-Frauenklinik, Erlangen, Germany)

An extensive statistical analysis is attempted which correlates dose to outcome. The work at recognized major centers (Zürich, Heidelberg, Copenhagen, Stockholm, Paris, Manchester, Rochester (Minn.), Berne, Erlangen) is evaluated and compared. Of particular interest are those tables in which one method is compared with another at the same institution. In several instances this was possible because a particular department switched from one method to another. In Berne, for example, the single dose method of Wintz was employed until 1931, when the fractionated Coutard method was adopted. The absolute cure rate has risen from 18.4 to 40.2 per cent since the change was effected. The results are also broken down according to the international staging classification, showing that improvement by fractionation is mainly confined to Stages II, III, and IV. Stage I exhibited good results with almost any method.

This analysis is too detailed to constitute a basis for general conclusions. It is eminently suited to tracing the influence of many different treatment factors upon the outcome.

The author concludes that the survival and the cure rates depend not only on the magnitude of the dose but also on its spatial and chronological distribution. Too high a dose causes the survival rates to drop "significantly."

Four diagrams; 3 graphs; 25 tables.

GERHART S. SCHWARZ, M.D.
New York, N. Y.

Thoughts of a Radiologist in a General Hospital on Cancer of the Bladder. Hans W. Hefke. J. Urol. **82:** 231–233, August 1959. (Marquette University School of Medicine, Milwaukee, Wisc.)

Basing his remarks on his experience as a radiologist in a general hospital, as well as on important papers on cancer of the bladder that have appeared in the urological and radiological literature in the past five years, the author examines some of the basic principles used in the multiple methods of irradiation applied to these tumors, reviews the results from different irradiation technics, and considers briefly the claims of surgery as against radiology. The radiation procedures are divided into four categories: (1) external irradiation; (2) interstitial irradiation; (3) intravesical irradiation; (4) a combination of surgical procedures with one of the irradiation methods.

According to the author, external radiation with conventional voltage cannot be considered as a definitive approach to the cure of cancer of the bladder and should be reserved for palliation only. Supervoltage, betatron, and external cobalt therapy are only briefly mentioned.

In respect to interstitial radiation, it is noted that postimplantation necrosis and late fibrotic cystitis probably explain the reluctance of some urologists to use this logical approach to localized tumors of the bladder. The statistically different results obtained with this method may well reflect differences in technical skill and knowledge of dosage calculation.

The most commonly used method of intravesical application of radiation sources at the present appears to be the Walter Reed technic, which depends upon a small central source of radium or cobalt 60 in a balloon applicator and makes use of the principle of dosage fractionation. The intravesical introduction of radioactive solutions into the bladder, such as isotopes of gold, sodium, bromine, or cobalt, does not, theoretically or practically, appear to show much promise.

The combination of any of the foregoing procedures with surgery, such as diathermy combined with radon implants, or surgical excision followed by irradiation, or irradiation followed by surgery, comprises the fourth method of treatment. Procedures such as radical cystectomy may be indicated when radiation methods

have failed or have produced intractable after-effects.

The incidence of five-year absolute arrests of bladder cancer with different treatment methods, as gathered from the literature, is as follows: 22.3 to 29 per cent after surgery only; 29 to 58 per cent after radon implants (with or without surgical procedures), and, 56 per cent or less following treatment by the Walter Reed method.

The author concludes that 25 to 50 per cent of patients with carcinoma of the bladder may be salvaged to the extent of five-year arrest. However, emphasis on successful therapy must be shifted to early diagnosis, and it is essential that some of the possible surgical and radiation procedures be tried and reported.

HORACE W. SCOTT, M.D.
University of Pennsylvania

Supervoltage Roentgentherapy: Clinical Evaluation Based on 2,000 Cases. Gilbert H. Fletcher. Texas State J. Med. **55:** 676–683, August 1959. (University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas)

Basing his opinion on a clinical evaluation of 2,071 cases, the author states that the improved curative value of supervoltage roentgen therapy is limited to those cancers that, while amenable to irradiation, have been poorly controlled locally by conventional methods. These would include the squamous-cell carcinomas of the oropharynx, the deeply infiltrative anaplastic tumors of the urinary bladder, and the late cancers of the cervix.

Supervoltage roentgen therapy can improve cure rates and permits easier definitive therapy for lasting control and short range palliation with less discomfort. It cannot allow retreatment because of risk of necrosis of inner structures, is useless in the management of radioresistant cancers, and does not influence the course of generalized cancer.

As compared with cobalt 60, supervoltage roentgen therapy produces less skin reaction with a greater depth dose, less side-scatter and radiant energy in penumbra, and better organ and systemic tolerance (less radiation sickness, less change in blood count, etc.), but requires a slightly higher tumor dose (10 to 15 per cent) and produces late fibrosis. Similarities between the two methods include: no specific action on tumor cells (radiosensitivity unchanged, for instance, in cancers of the gastrointestinal tract, glioma multiforme, etc.); no difference in differential sensitivity between tumor cells and normal cells; limitation of deep organ tolerance.

The integration of radiation and surgical procedures, such as radical neck dissections and radical mastectomies after irradiation, is decidedly improved by supervoltage roentgen therapy. Because of the skin-sparing factor, wound healing is less difficult.

The most striking advantage of supervoltage roentgen therapy is the absence of skin reaction. This characteristic, however, necessitates enlarged clinical experience and more careful physical planning, because the therapist is deprived of a traditional warning.

One graph; 7 tables.

RADIOISOTOPES

Beta Radiation Sources, Uses, and Dangers in Treatment of the Eye. Report to Council on Medical Physics, American Medical Association. William F. Hughes. J.A.M.A. **170:** 2096–2101, Aug. 22, 1959. (Department of Ophthalmology, University of Illinois College of Medicine, Chicago, Ill.)

Beta-radiation ophthalmic applicators, particularly the radioactive strontium (Sr^{90})-yttrium (Y^{90}) applicator, provide a ready source of radiotherapy for superficial lesions of the eye. The general indications for this type of treatment are the same as those for other forms of radiation, such as x-ray. Because the therapeutic dosage and the dosage which might result in later complications are fairly close, exact knowledge must be obtained concerning the output of the applicator in rads per second, the depth dose, biological standardization, and the differential sensitivity of the tissues to be destroyed compared with the normal ocular tissues. This is especially important when radiation is given over the limbus, which is only 3 mm. away from the sensitive equatorial region of the lens.

Minimal cataractogenic doses appear, at this time, to be approximately 5,000 rads at the applicator surface with the Sr^{90} applicator over the limbus. Minimal lens opacities in the periphery do not necessarily progress or affect vision, and certain serious ocular conditions requiring beta radiation warrant the necessary risk of producing a cataract later. In general, beta radiation should be reserved for use in those ocular conditions in which it is superior to other modes of treatment or in which other methods have failed.

Two tables.

Distribution of Serum Radioiodinated Compounds in Euthyroid and Hyperthyroid Patients Following Hypophysectomy. Sidney C. Werner, David V. Becker, and Vas V. Row. J. Clin. Endocrinol. **19:** 953–957, August 1959. (180 Ft. Washington Ave., New York.)

Previous reports on the effect of hypophysectomy upon the distribution of iodine in serum were based on animal studies. This report deals with patients undergoing hypophysectomy for cancer or Graves' disease.

The distribution of labeled iodide compounds in the serum was the same before and after hypophysectomy in patients with Graves' disease, but there was marked alteration of distribution in patients who underwent the same procedure for prostatic or mammary cancer. The clinical picture of hypopituitarism developed in all patients postoperatively.

These findings could be explained by the fact that the pituitary-thyroid relationship is abnormal in hyperthyroidism, and that hyperthyroidism can occur in patients having a greatly reduced mass of functioning anterior pituitary tissue. It is possible that a few remaining hyperactive pituitary cells were sufficient to keep the thyroid activated.

One table.

ZOLTAN SZALONTAY, M.D.
Mercy Hospital, Pittsburgh, Pa.

Alterations of Thyroid Function in Severe Heart Disease, as Measured by I^{131} Techniques. Wade N. Miller and Lillian E. Jacobson. J. Clin. Endocrinol. **19:** 949–952, August 1959. (Radioisotope Department, Presbyterian Hospital, Newark, N. J.)

A study of 18 patients with severe heart disease

following administration of an I^{131} tracer showed the following results in thyroid function compared with euthyroid controls: The thyroid uptake of I^{131} was the same as in euthyroid subjects; the PBI^{131} plasma level was decreased at twenty-four and seventy-two hours; the twenty-four hour conversion ratio was decreased; the salivary I^{131} activity was increased at twenty-four hours.

The decrease in PBI^{131} would seem to indicate that thyroid hormone synthesis has been impaired, and the decrease in the conversion ratio reflects both the decrease in plasma PBI^{131} and the increase in inorganic I^{131} content. The increase in salivary radioactivity does not appear to be merely a reflection of the increase in the inorganic iodine level of the plasma, for the ratio between salivary activity and the plasma inorganic iodine activity is not constant but varies with the disease state.

Data on hyperthyroid and hypothyroid patients are listed for comparison.

Two tables. ZOLTAN SZALONTAY, M.D.
Mercy Hospital, Pittsburgh, Penna.

External Counting of Ca^{47} and Sr^{85} in Studies of Localised Skeletal Lesions in Man. Göran C. H. Bauer and Bo Wendeberg. J. Bone & Joint Surg. **41-B:** 558–580, August 1959. (Lund University, Malmö, Sweden)

The use of external counting technics using Sr^{85} and Ca^{47} in man furnish useful data for study of problems in bone metabolism, quantitation of the accretion rate of normal bone or bone lesions, and localization and delineation of skeletal lesions.

A dose of either isotope, 60 microcuries or less, is given either intravenously or intramuscularly and a scintillation counter with a sodium iodide crystal, linear amplifier, single channel analyser, and convertible collimator were used. Body-surface countings were made with the aperture of the collimator close to the skin and, when the measurements were made over the limbs, corresponding sites over the right and left side were always counted in order to permit comparison of a diseased region with a normal region.

The counting rate over fractured bone was uniformly higher than over corresponding normal bone, with the fractured/normal counting rate ratios ranging from 5 to 12. These initial counting rate ratios tend to increase during the first six or eight weeks after fracture, and then gradually decrease.

Elevation of the right/left hip counting rate ratio enabled the experimenter to detect a fracture of the right femoral neck which was not visualized on the initial radiographs.

Both malignant and benign bone tumors showed a higher Ca^{47} or Sr^{85} uptake in the tumor area than in normal bone. On one occasion, it was possible to detect a metastatic lesion in one lumbar vertebra before it was seen on the radiograph. The number of cases is too small, however, to allow any analysis of isotope uptake pattern in different types of malignant and benign bone tumors.

The counting rate over the lesions in several cases of Paget's disease was persistently higher than over normal bone by a factor of about 6. Blood volume determination in the affected area showed this high ratio to be mainly due to high uptake of Ca^{47} in bone.

In two cases of osteomyelitis, higher counting rates over the osteomyelitic lesions were noted.

The external counting rate recorded over any part of the body is proportional (by a factor k) to the amount of activity contained with that part. The proportional factor k varies from one anatomical region to another. It is influenced by factors related to the amount of tissue "seen" by the counter, by the density of this tissue and the distribution of isotope in it, by calibration of the counting equipment, and by the energy of the isotope counted.

The external counting rate ratio would equal the accretion rate ratio if the numerical value of the exchangeable space were proportional to the numerical value of the accretion rate in a given part of the body. This deduction is based on a series of assumptions, the validity of some of which is as yet poorly established.

No satisfactory results have been obtained with the use of radiosodium and radiogallium in the study of bone metabolism or localization of bone lesions. However, it has been shown that barium 140, in man, is handled by bone in about the same way as are calcium and strontium, and might therefore be used for external counting studies over the skeleton.

Fourteen roentgenograms; 14 diagrams; 23 graphs; 5 tables. FREIDOUN ESKANDARI, M.D.
Cleveland Metropolitan General Hospital

A 250-Curie Caesium 137 Unit Designed for Low Dosage Rates at Short Source to Skin Distances. G. F. Whitmore and H. E. Johns. Brit. J. Radiol. **32:** 533–538, August 1959. (Ontario Cancer Institute, Toronto, Ont., Canada)

A cesium-137 therapy unit containing 260 c in a source 1.5 cm. in diameter is described. The treatment distance is 15 cm. The source is mounted on a wheel 13 cm. in diameter. In the "off" position, the source is surrounded on all sides by a minimum of 12.5 cm. of heavy metal. Measurements have shown the dose rate on the surface of the head of the unit to be from 2 to 10 mr/hr, with an average of 4 mr/hr. When the unit is "on," radiation outside the room is less than 1 mr/hr. Lead treatment cones 7 cm. long, closed by a layer of stainless steel 0.023 in. thick, provide collimation.

The relative dose rises from 80 per cent at the surface to 100 per cent at 0.15 cm. depth. Depth-dose curves, including that for 0 field, plotted on semilog paper, are concave upward. The explanation is that at this short treatment distance the inverse-square law is more important than absorption.

The depth-dose values are almost the same as those obtained for a similar unit containing Co^{60}, because of the importance of the inverse-square law. Therefore, the longer half-life and smaller head required for the same protection give cesium the advantage over cobalt.

Six figures; 2 tables. LUCILLE DU SAULT
The Henry Ford Hospital

A Small Department for the Clinical Application of Radioisotopes. Paul-Otto Buchhorn and Dietrich Frost. Strahlentherapie **107:** 321–333, October 1958. (In German) (Städtische Rudolf Virchow-Krankenhaus, Berlin, Germany)

The floor plan and equipment of the isotope department of the Rudolf Virchow Hospital of Berlin are described. This is a 1,200-bed hospital and with the exception of neurosurgery, all medical specialties are represented within it. It was decided to limit use of

isotopes to clinical application and research and forego labeling procedures such as might be needed in biological laboratories. The principal activities of the department are: thyroid function testing, thyroid localization, thyrotherapy, circulatory testing including blood volume, etc., liver function studies, localization of liver tumors, demonstration of block in the spinal canal, therapy of blood dyscrasias and metastases, intracavitary instillation of radiogold, local therapy with radiogold, surface therapy. The average working load is 95 patients per month (more than 200 procedures).

Photographs are impressive and show modern equipment in clean bare rooms, practically distributed. The number of instruments is large. Detailed information is given on sewage disposal, cross section of water pipes, safety features, etc.

[In the abstractor's opinion, this department is a model after which many an American department should be fashioned. It is doubtful that there is a single hospital in the United States of similar size which possesses a comparable isotope department. The article should provide ammunition to radiologists who have to negotiate with hospital administrators. It is "must reading" for radiologists who are department heads.—G. S. S.]

Seven figures. GERHART S. SCHWARZ, M.D.
New York, N. Y.

RADIATION EFFECTS

Illustrations and Reports of Late Effects of Radiation. A. G. S. Cooper. M. J. Australia **2**: 267–271, Aug. 29, 1959. (Queensland Radium Institute, Brisbane, Australia)

The paper is a very general one, summarizing data reported by others on late effects of irradiation, both genetic and somatic. Discussion and pertinent information are given relative to the following subjects:

1. Tissue effects, including blood changes, in patients, in medical and industrial radiation workers, and in persons exposed accidentally in atomic warfare.
2. Effects on the fetus following irradiation of the mother, including leukemia as a possible sequel to exposure.
3. Genetic hazards.

The material presented will be of interest to those desiring background information on radiation hazards. Pertinent data published by others are summarized in tables, and statistical analyses show the incidence or probability of adverse effects from various applications of radiant energy.

The author concludes with an outline of "safeguards for the future" including ways in which radiation exposures can be controlled and decreased without impairing their medical usefulness.

One graph; 5 tables. JAMES W. BARBER, M.D.
Cheyenne, Wyo.

Radiation Hazards of Diagnostic X Rays. Alice Stewart. M. J. Australia **2**: 265–267, Aug. 29, 1959. (Oxford, England)

The author analyzes data available from hospital records, private physicians' records, and information from the Office of Vital Statistics in an effort to evaluate the possible hazards of diagnostic x-rays in the production of leukemia in children and cancer in adults. It is admitted that the study is not one of planned experiment, but rather a "medical survey" or a "desk work analysis whose end-point is a demonstration of statistical relationships between presumed risk factors and presumed medical consequences."

There were collected 1,299 cases of cancer or leukemia in children considered sufficiently documented and adequately studied for inclusion in this report. The survey included interviews with mothers as well as a "control study" with data obtained from presumably normal children of the same age picked at random. Much discussion is given as to the background of the survey and the types of interviews and case material utilized.

The major conclusions are that prenatal exposure to x-rays increases the risk of subsequent development of leukemia or cancer, and that at a particular age the risk of carcinogenesis resulting from diagnostic x-ray examination is definite but small. Additional findings include the fact that first-born children and children born to mothers forty years of age or older are more likely to die of malignant disease than other children. There is a peculiar and as yet undetermined linkage between mongolism and leukemia. Recovery from acute pulmonary infection is occasionally followed by the development of leukemia. The peak mortality rate from this type of disease lies between the ages of two and four years.

The author comments briefly on a similar study of adult leukemia and its possible relationship to diagnostic radiologic procedures. Although the study is incomplete there appears to be a remarkable similarity between the findings in adults and children. For adults, the author feels that a definite increase in leukemia can be shown for individuals who have received 20 or more diagnostic x-ray examinations of the limbs, or who have undergone radiotherapy directed toward a thoracic or abdominal organ.

No data are given in this report.

JAMES W. BARBER, M.D.
Cheyenne, Wyo.

Radiation Cataract Following Fractionated Radium Therapy in Childhood. C. F. Qvist and B. Zachau-Christiansen. Acta radiol. **51**: 207–216, March 1959. (Radium Centre, Copenhagen, Denmark)

In their investigation of radiation cataract, the authors reviewed 855 cases of hemangioma in the region of the head, which had been treated with radium during 1913 and 1933. Of this number, 112 were found to have received a lens dose of more than 100 r; and 57 of these patients were traced and examined. In 4, radiation cataract had developed; 3 had impaired visual acuity, and the percentage of those having relatively marked refraction anomalies was 19 per cent as compared to 2 per cent statistically expected.

The authors discuss the literature pertaining to the subject and present their own cases in tabular form. They found the minimum cataractogenic lens dose to be 1,380 r. The maximum noncataractogenic dose for infants was 900 r, and for children of school age 1,140 r.

Five tables. JULIAN O. SALIK, M.D.
Baltimore Md.

Radiation Induced Dysplasias of Bone. Philip Rubin, J. Robert Andrews, Richard Swarm, and Hazel Gump. Am. J. Roentgenol. **82:** 206–216, August 1959. (Strong Memorial Hospital, Rochester 20, N. Y.)

The authors report an experimental study on the effect of radiation on bone and cartilage in rats. Irradiation was applied by two methods: (1) internally by radioactive isotopes and (2) externally. The internally administered isotopes, Y^{90}, Sr^{90}, and P^{32} (which are beta emitters), and radium and plutonium (alpha emitters) are deposited in the zones where cartilage and osteoid are calcified and are laid down in the place of calcium phosphate apatites, which are the mineral building blocks of bone. Cartilaginous and osteoid calcifications are disturbed. Osteoblasts disappear from the epiphyseal line, and cartilage production is decreased. Temporary arrest of linear growth occurs, and growth processes after resumption are slower and more abnormal. Roentgenograms show a dense white line in the shaft which presumably is "old spongiosa" and marks the metaphyseal area at the time of insult.

The cartilage seeker, S^{35}, is deposited in the ground substance of cartilage as chondroitin sulfate, and under the influence of irradiation cartilage proliferation ceases. Not only is bone growth halted but the modeling of bone is profoundly altered. There is absence of tubulation, resulting in rectangular shaped bones.

External irradiation of whole bones resulted in cessation of growth of bone and cartilage. The irradiated bones became fragile and excessively tubulated. Irradiation limited to the epiphyses caused shorter, narrower bones, with appearances suggestive of achondroplasia. When only the metaphyses were irradiated, the result was bowing but very little decrease in length and slight lack of tubulation. External irradiation of the diaphyses resulted in narrowed bones of normal length with fibrotic marrow cavities.

Thirteen roentgenograms; 2 autoradiographs; 3 photomicrographs; 3 photographs; 4 diagrams; 1 graph.

PAUL MASSIK, M.D.
Quincy, Mass.

Ionizing Radiation and Public Health. Herman E. Hilleboe. Texas State J. Med. **55:** 670–676, August 1959. (New York State Department of Health, Albany, N. Y.)

This paper opens with a general appraisal of the problem of exposure to ionizing radiation in its relation to public health and goes on to discuss the situation in New York State and some of the measures that have been adopted there for its solution. It is estimated that if all medical practitioners in the state could manage to expose patients to an average of 10 per cent less radiation than at present, still doing the same amount of good, 1,700 lives of seventy years each would be saved over a thirty-year period. By taking postgraduate courses in radiologic diagnosis, therapy, and protection, and exercising all due precautions the physician can play a leading role in the long-range public health program.

In New York State a regulation adopted in July 1958 prohibits the use of radiation by anyone not licensed or authorized to practice medicine, dentistry, podiatry, or osteopathy. The registration of radiation sources is required, as is notification when such sources are either newly installed or moved to another site. The Health Department has provided an advisory service to users of radiation and is performing a schedule of inspections limited only by the number of trained personnel in state and local health departments. Through the Air Pollution Control Board, 15 air sampling sites are maintained, at each of which sampling of natural background levels is made. The Health Department's Division of Laboratories and Research analyzes for radioactivity water samples from public water supplies throughout the state. Six fall-out stations determine total state-wide fall-out from dust and precipitation each week. Present plans include the examination of milk samples at monthly intervals from five selected milk sheds throughout the state.

The state has undertaken a survey around a proposed site of nuclear installation before its establishment to determine the normal radioactivity of the area. When operations begin, the state will maintain regular inspection of the plant and environs.

Whether or not large states should own and control a site to dispose of high level radioactive wastes from industrial installations is a matter for serious consideration. Arguments for such a program are that it would ensure safe control of such sites in perpetuity and would encourage nuclear industries to locate within the state.

Some Prompt and Delayed Effects of X Rays on Growth of Human Amnion Cells (Strain FL) in Tissue Culture. Henry I. Kohn and Jørgen E. Fogh. J. Nat. Cancer Inst. **23:** 293–304, August 1959. (University of California School of Medicine, San Francisco, Calif.)

Some prompt and delayed effects of single doses of 100-kv x-rays on the growth of the established FL strain of human amnion cells in tissue culture were studied. The parameters of growth measured were cell volume, number of cells per culture, and total volume of cells per culture (culture volume). The effects were dependent on x-ray dose.

Small changes in the growth rate were observed after 100 r, but sterilization of the culture required 1,500 to 2,000 r. Growth in cell number was more sensitive to radiation than growth in cell volume; thus irradiation tended to produce a condition of continued cellular growth accompanied by mitotic inhibition. As a result, the distribution of cell volumes was widened and the entire distribution was shifted toward higher values. Giant cells represented the largest size in the changed distribution.

Subcultures from irradiated cultures that had received 100 to 600 r grew out readily. After 1,000 r, an exponential growth curve similar to that for unirradiated cultures was obtained after several transfers. The x-ray sensitivity of such "1,000 r-recovered" cultures was not strikingly different from that of the unirradiated cultures. The latter, however, had a less pronounced latent period. The recovery of such irradiated cultures involved, *inter alia*, the elimination of damaged cells by a process that may be considered analogous to natural selection. The bearing of this phenomenon on the prompt and late effects of x-rays *in vivo* is discussed briefly.

Six figures; 1 table. AUTHORS' SUMMARY

X-Ray Effects on Mitotic Activity of the Accessory Sex Organs of Castrate Rats Stimulated by Testosterone Propionate. John H. D. Bryan and John W. Gowen. Biol. Bull. **117:** 68–80, August 1959. (Department of Genetics, Iowa State College, Ames, Ia.)

The accessory organs of castrated male rats were

used in a study of the effects of x-rays on mitosis in somatic tissues.

Animals nine weeks old were castrated and the organs allowed to regress for twenty days prior to use. Half the animals received daily injections of 500 μg. of testosterone propionate (in oil) until death; the others, in addition to the hormone injections, were exposed to a single dose of 320 r of x-rays, the irradiation being given at the time of the first hormone injection. Pairs of animals were killed at twenty-four, forty-eight, sixty, and seventy-two hours following the irradiation and/or initial hormone treatment.

The response to the treatments was followed by means of mitotic index determinations and cytophotometric measurements of the DNA-Feulgen content of interphase nuclei.

The cytological data indicate the existence of a difference in response between the epithelium of the seminal vesicle and of the dorsal prostate. At no time during the experiment did the mitotic activity of the latter rise to levels characteristic of the former. In addition, the time-response curves for the two organs indicate that the dorsal prostate responds more slowly than the seminal vesicle.

The DNA-Feulgen measurements together with the mitotic index data indicate that in the controls and in the experimental animals killed prior to forty-eight hours there is a close correspondence between the level of mitotic activity and the rate of chromosomal reduplication. Over the period of forty-eight to seventy-two hours in the case of the dorsal prostate the data show that, during the time of maximal hormonal stimulation, DNA synthesis is proceeding at a rate appreciably faster than the rate at which nuclei enter into prophase.

The results obtained have been compared with those obtained from a similar experiment involving the mouse testis. The accessory organs appear to be less sensitive to the irradiation than the testis. The present results, together with the authors' earlier data on the mouse testis, not only imply that the male germ line may differ from somatic tissues in its response to irradiation, but also that somatic tissues may differ from one another in this respect. At the present time, it would appear that differences between the tissues studied are mainly ones of degree and rate of response. However, the findings of Pelc and Howard (Exper. Cell. Res. **11**: 128–134, 1956) point to the possibility that somatic and germinal tissues may also differ in their metabolic pathways. Until more biochemical and cytological information is at hand, the precise nature of these differences must remain an open question.

One figure; 3 tables. AUTHORS' SUMMARY

Comparative Effects of Intraperitoneal and Oral Administration of AET on Survival of X-Irradiated Rats. Rodney L. Preston, Arthur F. Wells, and Benjamin H. Ershoff. Radiation Res. **11**: 255–259, August 1959. (R. L. P., Aero Medical Laboratory, Wright-Patterson Air Force Base, Ohio)

Available data indicate that the intraperitoneal administration of S, 2-amino-ethylisothiuronium·Br·HBr (AET) shortly before exposure to a lethal dose of total-body x-irradiation protected against radiation death in the mouse and monkey, but was without significant effect on survival in the dog. The authors report an investigation of the effects of intraperitoneal and oral administration of graded levels of AET on the survival of rats exposed to a dose of 900 r of total-body x-irradiation, a dose which was lethal for unprotected rats.

Intraperitoneal administration of AET at a level of 300 mg./kg. of body weight shortly before exposure to irradiation resulted in a highly significant increase in length of survival. When given by intraperitoneal injection at a level of 400 mg./kg. of body weight, however, AET not only failed to increase but actually decreased survival as compared to that of untreated controls. In contrast to the results obtained with intraperitoneally administered AET, oral administration of AET by stomach tube (at levels of 400 or 800 mg./kg. of body weight) shortly before irradiation or mixed in the diet and fed at graded levels (1, 2.5, 5, or 10 gm./kg. of diet) prior to and after irradiation was without significant effect in increasing the survival of irradiated rats.

Two tables.

Recovery from Partial-Body X-Irradiation as Measured by the Lethality of Two Exposures. Arland L. Carsten and Thomas R. Noonan. Radiation Res. **11**: 165–176, August 1959. (A. L. C., Brookhaven National Laboratory, Upton, L. I., N. Y.)

For the purpose of studying recovery from partial-body x-irradiation, the efficiencies of various shielding procedures were evaluated in rats. A double wrap-around shield, which proved to be the most efficient, reduced the rate to about 1 per cent of the outside dose at a distance of approximately 6 cm. from the edge of the shield. These studies, together with appropriate dissections, permitted estimates of dosages to various organs under the conditions of exposure employed.

The LD 50's for upper-body, lower-body, and whole-body irradiation were found to be 1,750 r, 1,080 r, and 750 r, respectively. These values are similar to those reported by Bond and co-workers (see, for example, Radiation Res. **1**: 241, 1954. Abst. in Radiology **64**: 633, 1955).

By using two partial-body exposures to x-radiation, separated by various time intervals, the pattern of recovery (as measured by lethal effects) was determined for lower- and upper-body irradiation. The recovery from a lower-body exposure of 648 r can be expressed by a single exponential function with a half-recovery time of 1.7 days. The recovery from an upper-body exposure of 1,300 r can be expressed by a single exponential with a half-recovery time of 7.0 days or by two exponentials, one with a half-recovery time of 3.8 days and the second with a half-recovery time of 7.5 days.

Four figures; 4 tables.

Lymphocyte Depletion of the Blood and Bone Marrow of the Irradiated Rat: A Quantitative Study. E. V. Hulse. Brit. J. Haematol. **5**: 278–283, July 1959. (Atomic Energy Research Establishment, Harwell, Berkshire, England)

The reductions in the numbers of lymphocytes in the blood and in the bone marrow of the rat from two to forty-eight hours after exposure of the whole body to various doses of x-radiation are described. The blood showed a greater depletion than did the bone marrow, and it is suggested that the results support the concept that the radiosensitivity of lymphocytes is dependent on their age and environment.

In both blood and marrow, a bimodal time response was found after medium and large doses, a rapid depletion for the first sixteen to twenty-four hours being followed by a much slower depletion at later time intervals. It is concluded that the depletion is caused by two different processes. The initial rapid phase is thought to be due mainly to the actual killing of lymphocytes by irradiation, and the slower phase to a reduction in the production of new lymphocytes.

Three graphs. AUTHOR'S SUMMARY

Transplantation of Homologous and Heterologous Lymphoid Cells in X-Irradiated and Nonirradiated Mice. O. Vos, M. J. De Vries, J. C. Collenteur, and D. W. Van Bekkum. J. Nat. Cancer Inst. **23:** 53–73, July 1959. (National Defense Research Council TNO, Rijswijk Z. H., The Netherlands)

The injection of a large number of homologous lymphoid cells kills x-irradiated mice protected with isologous or homologous bone marrow, within one to two weeks. The injection of a smaller number of homologous lymphoid cells kills the mice after a longer interval. Parental-strain lymphoid cells have a detrimental effect in irradiated F_1 hybrids, but F_1 hybrid lymph-node cells produce no ill effect in parental strain mice.

Rat lymph-node cells have a lethal effect in irradiated mice protected with heterologous bone marrow only when the cells are injected at twenty-four hours after irradiation.

On the basis of the number of cells required to produce a certain percentage of mortality, homologous lymph-node cells are somewhat more effective than homologous spleen cells, but much more effective than homologous thymus cells. Mice that died ten to twenty days or later after injection of homologous or heterologous lymphoid cells had symptoms and lesions which resembled those seen in mice that died from the secondary disease after foreign bone-marrow transplantation. A pathological syndrome resembling the secondary disease has been evoked in a certain number of nonirradiated F_1 hybrid mice by the injection of a large number of lymphoid cells from parental strain mice that had been sensitized against iso-antigens of the other parental strain. These observations support the concept of a graft-antihost reaction that is involved in the development of secondary disease.

Three photographs; 5 graphs; 7 tables.

AUTHORS' SUMMARY

Effect of Continuous Gamma Irradiation of Mice on Their Leukocyte Counts and Susceptibility to Bacterial Infection. Carolyn W. Hammond, Sonia K. Anderle, and C. Phillip Miller. Radiation Res. **11:** 242–252, August 1959. (Department of Medicine, University of Chicago, Chicago, Ill.)

Ten-week-old CF-1 female mice were exposed continuously to γ-radiation (from a cobalt-60 source) at three dose levels: approximately 34, 72 to 67, and 130 to 127 r per day. Leukocyte counts (total and differential) and red cell volumes were followed and at intervals susceptibility to bacterial infection was determined by intraperitoneal challenge with graded inocula of *Pseudomonas aeruginosa*.

Increased susceptibility to this infection was found to be related to the rate of irradiation rather than the total amount accumulated. At the lowest dose rate (34 r per day), the accumulation of 2,140 r during nine weeks produced practically no increase in susceptibility to the experimental infection. At the next higher dose rate (72 to 67 r per day) susceptibility began to increase after the third week. It was manifested principally by deaths among mice receiving smaller and smaller inocula of the test microorganism. At the highest dose level employed (130 to 127 r per day) susceptibility increased more rapidly.

The development of leukopenia and anemia was also related to the rate of irradiation rather than the total amount accumulated.

Two figures; 5 tables.

The Differential Action of Irradiated and Chemically Treated Marrow on Survival and on Thymic Regeneration in Irradiated Mice. Irwin Berman and Henry S. Kaplan. Radiation Res. **11:** 24–29, July 1959. (Stanford University School of Medicine, San Francisco, Calif.)

This report is concerned with experiments in which bone marrow subjected to pretreatment known to render it ineffective in promoting thymic regeneration was assessed for its capacity to protect against lethal doses of x-irradiation.

Bone marrow from donor mice pretreated with x-rays, thio-TEPA (triethylenethiophosphoramide) and urethan failed to promote thymic regeneration in sublethally irradiated animals, while the same number of cells from the same marrow pools were effective in protecting against the effects of lethal doses of irradiation.

The implications of these results are discussed. It is concluded that there are at least two factors or mechanisms of action by which bone marrow independently promotes thymic regeneration and survival in x-irradiated animals. It is considered highly unlikely that isologous bone marrow promotes thymic regeneration simply by repopulating the irradiated thymus gland.

Three tables.

Energy Absorption by the Bone Marrow of the Mouse Receiving Whole-Body Irradiation with 250-Kv X-Rays or Cobalt-60 Gamma Rays. E. R. Epp, H. Q. Woodard, and H. Weiss. Radiation Res. **11:** 184–197, August 1959. (Sloan-Kettering Institute, New York, N. Y.)

The problem of determining the relative efficiencies of radiations of different qualities in causing the death of mammals after whole-body exposure is complicated by difficulties in estimating the energy absorbed by the bone marrow. This may be greater than the energy absorbed by soft-tissue parts distant from bone, inasmuch as bone contains elements of higher atomic number than are present in soft tissue, and therefore has an increased photoelectric absorption coefficient. A proportion of the large number of photoelectrons set in motion in bone cross the interface and deposit their energy in the adjacent marrow. This contribution is absent in soft-tissue elements beyond the range of the photoelectrons. The effect is greater for 200- to 300-kvp x-rays than for 1,000-kvp x-rays or for the γ-rays of radium or cobalt 60, because of the strong inverse dependence of the photoelectric absorption coefficient with energy.

A physical model was constructed to represent the spatial relationships between mouse marrow and the bones enclosing it. With this model, detailed calcula-

tions were made of the energy absorption in marrow cavities of various sizes and shapes during whole-body exposure to 250-kv x-rays or cobalt-60 γ-rays. The calculations involve a double integration over all photon and electron energies concerned.

The average energy absorption by the total marrow of the mouse subjected to whole-body irradiation was calculated to be 98.6 ergs/c.c./r from 250-kv x-rays and 94.0 ergs/c.c./r from cobalt-60 γ-rays.

The significance of this difference in absorbed energy in interpreting the relative biological effectiveness of the two radiations is discussed.

Eight figures; 3 tables.

The Pathogenesis of the Secondary Disease After Foreign Bone Marrow Transplantation in X-Irradiated Mice. D. W. Van Bekkum, O. Vos, and W. W. H. Weyzen. J. Nat. Cancer Inst. **23:** 75–89, July 1959. (National Defense Research Council TNO, Rijswijk Z. H., The Netherlands)

The available information on the pathogenesis of the secondary disease after foreign bone-marrow transplantation in irradiated mice is reviewed. Additional experiments are reported.

The incidence of secondary disease after foreign bone-marrow transplantation in mice was studied in various host-donor combinations after irradiation at three dosage levels. A characteristic secondary mortality was observed in CBA mice that received isologous bone marrow after the larger doses of x-rays. Secondary mortality did not occur in F_1 hybrid mice that received isologous bone marrow, but severe diarrhea developed after the higher doses of x-rays when followed by treatment with parental-strain bone marrow.

In mice treated with rat bone marrow, the development and persistence of symptoms of secondary disease were correlated with the presence of a functional rat bone marrow.

Skin lesions and wasting, typical of secondary disease, as well as a high rate of mortality, were observed in F_1 mice after the establishment of a parabiotic junction with a parental strain mouse of the same sex and age.

Evidence is provided in support of the hypothesis that the secondary disease in mice treated with foreign bone marrow is due to the combined effects of late radiation damage, an immunological reaction of the graft against the host, and an impaired immunological defense against microorganisms.

Two photographs; 2 charts; 3 tables.

AUTHORS' SUMMARY

Immunogenetic Studies on X-Irradiated Mice Treated with Hematopoietic Cells and Grafted with Tumor Tissues. Michael Feldman and David Yaffe. J. Nat. Cancer Inst. **23:** 109–131, July 1959. (Weizmann Institute of Science, Rehovoth, Israel)

A study was made of the behavior of tumor grafts in the radiation chimera to analyze the immune reactivity of the donor's hematopoietic cells and the influence on tumor cells of the radiation chimera. The regression of homografts of sarcoma C10 and sarcoma MC1M (of C3H origin) in irradiated C57BL animals treated with C57BL cells and their progressive growth in irradiated animals treated with C57BL fetal hematopoietic cells gave evidence of the ability of donor cells to form transplantation immunity against foreign antigens, thus substantiating the graft versus host theory as the basis for "homologous secondary disease." Tumor grafts produced metastases in irradiated animals, and irradiation and immunogenetic factors were shown to influence their development.

The transplantation of sarcoma SBL1 into various types of genetic chimeras was accompanied by immunogenetic changes in the tumor, which were manifested by the loss of strain specificity. The effect of total-body irradiation of the host and the absence of isologous C57BL cells were shown to be the main factors determining this change. Their analysis provided definite indications that the acquired homotransplantability of SBLx sublines is basically a result of immunogenetic transformation induced by the host and not a result of selection of pre-existing compatible cell variants.

Two photographs; 1 chart; 7 tables.

AUTHORS' SUMMARY

Immunogenetic Changes Induced in Tumors Grown in Radiation Chimeras. David Yaffe and Michael Feldman. J. Nat. Cancer Inst. **23:** 133–151, July 1959. (Weizmann Institute of Science, Rehovoth, Israel)

An analysis was made of the immunogenetic properties of SBLx tumor lines that had acquired homotransplantability by growing in "radiation chimeras." This study mainly concerned the nature of the induced change and the mechanism of homotransplantability acquired. The SBLx tumors had lost the original antigenicity of SBL1, and their homotransplantability was thus based on inability to elicit an immune response. SBLx homografts, however, were found to be highly susceptible to transplantation immunity. Thus, the low antigenicity of the tumor cells was not due to the loss of the H antigens, but was attributed to a low rate of antigen emission. The analysis of these properties provided evidence that the change of SBL1 to SBLx involved a genetic transformation induced by the conditions that prevailed in the radiation chimeras.

The acquired homotransplantability was found to be a reversible process. Transplantation of SBLx tumors back into C57BL or into (C3H x C57BL)F_1 mice resulted in a complete loss of homotransplantability. The mere existence of the isologous C57BL antigens in the host was sufficient to produce this reversed change, and the SBLxB1 tumors thus formed regained the original antigenicity of SBL1. This reversed process took place only if the SBLx tumor was transplanted to hosts of foreign strains following nine to sixteen days of growth in C57BL mice. Prolonged growth of the tumor in C57BL mice did not result in the loss of strain specificity.

The significance of these data in relation to the possible mechanism of the reversible change is discussed.

Eleven tables. AUTHORS' SUMMARY

The Ability of Extrinsic Gonadotropin (FSH) to Function When Administered after Sublethal and Lethal X-Ray Exposures. J. F. Spalding, S. B. Hawkins, and V. G. Strang. Radiation Res. **11:** 67–71, July 1959. (Los Alamos Scientific Laboratory, Los Alamos, N. Mex.)

The germinal tissue and germ cells of the gonads, which function or fail to function as a result of hormonal stimulation, are considered to be among the most radiosensitive units of the mammalian organism. The ovulation process in the mammal includes the synergistic involvement of the gonadotropic hormones and gonadal tissues and cells. For this reason, the authors felt that an experiment designed to determine

the threshold dose of x-irradiation required to prevent fulfillment of the normal estrus cycle (ovulation) in the female mouse might help to establish the point where the interaction of the gonadal hormones and tissues is interrupted.

Mature female mice were treated with an intraperitoneal injection of 3.75 mg. of extrinsic gonadotropin (FSH) either just prior to or immediately after total-body x-ray exposure of 300 to 19,200 rads. Sixteen to eighteen hours after treatment, the mice were killed and the number of ovulations was determined. At above lethal doses, where induced ovulation was prevented, follicular ova were observed to determine the stage of maturation.

X-ray exposures up to and including 12,000 rads did not inhibit ovulation. Doses of 13,200 to 14,400 rads reduced the number of ovulations, and a dose of 19,200 rads prevented ovulation. There was much evidence to indicate that ovulation was blocked at 19,200 rads by damage to the estrogen-producing tissue.

Three photomicrographs; 1 table.

Effect of X-Irradiation on Plasma, Liver, and Bone Marrow Lipids of the Rabbit. E. E. Elko and N. R. Di Luzio. Radiation Res. **11**: 1–6, July 1959. (University of Tennessee Medical Units, Memphis, Tenn.)

An investigation of the lipid composition of bone marrow was undertaken to ascertain if bone-marrow lipids contribute to post-irradiation hyperlipemia and to evaluate the response of the various tissue lipid fractions to ionizing radiation.

Plasma, liver, and bone-marrow lipid fractions of 32 rabbits were determined twenty-four hours after 1,000 r of whole-body x-irradiation. Plasma phospholipid, cholesterol, and total lipid fractions in the irradiated groups were markedly elevated above the control values. Although no alteration was found in liver cholesterol concentration, liver phosphatide and neutral fat fractions were significantly increased in the irradiated group. The cholesterol, phospholipid, and neutral fat fractions of bone marrow, obtained either from the femur or from other bone-marrow sites, showed no significant alteration in the irradiated group. These findings indicate that bone-marrow lipids do not contribute to post-irradiation hyperlipemia, nor are they markedly altered twenty-four hours after lethal whole-body x-irradiation.

Three tables.

Recovery of X-Irradiated Rabbit Lenses. E. F. Riley, R. D. Richards, and P. J. Leinfelder. Radiation Res. **11**: 79–89, July 1959. (College of Medicine, State University of Iowa, Iowa City, Iowa)

Previous experiments by the authors showed recovery of the rabbit lens, even after exposures of 11,000 rads of x-irradiation, if a portion including at least one-fourth of the peripheral epithelium were shielded. Opacification of the partially shielded lens did not become complete while complete opacification occurred after similar exposure of the entire lens. A few partially shielded lenses were observed for as long as three years after irradiation. While it was demonstrated that a shielded portion was essential for recovery, it was not determined how this portion contributed to the recovery or how complete the recovery was.

In the present investigation, one half of a lens was exposed to 11,000 rads, and, at various times afterward, the second half was also exposed to 11,000 rads. If the interval between exposures was three months or less, the resultant opacification invariably became complete. When the interval was four months or more, the lenses generally did not become completely opaque. Accordingly, it is presumed that the first half had recovered sufficiently in four to five months to sustain the lens and make a recovery possible when the second half of a lens was in turn irradiated.

Three figures; 1 table.

Influence of Oxygen Tension on X-Ray-Induced Chromosomal Damage in Ehrlich Ascites Tumor Cells Irradiated in Vitro and in Vivo. Eleanor E. Deschner and L. H. Gray. Radiation Res. **11**: 115–146, July 1959. (L. H. G., Mount Vernon Hospital, Northwood, Middlesex, England)

In Part I of this paper the authors report investigations which they believe establish that the relation between sensitivity and dissolved oxygen has the same form for Ehrlich ascites tumor cells as for microorganisms, and that the constant, K, for cells irradiated at room temperature, is of the same order and possibly identical with the value 4 μ M/l recorded for the microorganisms (Howard-Flanders and Alper: Radiation Res. **7**: 518, 1957). In Part II, the measurements of oxygen tension and radiosensitivity are presented and discussed in relation to the behavior of the cells under *in vitro* conditions.

[For a review of the subject of oxygen tension in radiotherapy, see the article by Howard-Flanders and Scott in this issue of Radiology, p. 956.]

Eleven figures; 6 tables.

Physiological and Biochemical Studies on Various Species Exposed to Massive X-Irradiation. Douglas E. Smith and John F. Thomson. Radiation Res. 11: 198–205, August 1959. (Division of Biological and Medical Research, Argonne National Laboratory, Lemont, Ill.)

Diverse species of animals, including rats, mice, hamsters, bats, chickens, frogs, and lizards, were exposed continuously to x-radiation at dose rates of 450 to 500 r/min. until death. All the species irradiated at 23° C. died after accumulating a dose of approximately 100,000 r. A similar lethal dose was found in the case of poikilotherms irradiated in environments of 5 and 37° C. Decreases in rectal temperature up to 10° C. occurred during the irradiation of homeotherms at 23° C. After accumulating doses of about 15,000 r, bats irradiated at 5° C. showed spontaneous motor activity, increase in rectal temperature, and increase in oxygen consumption.

No significant alterations were observed in enzyme activities of irradiated tissues which could explain the mechanism of lethal action. The capacity of the rat brain for anaerobic and aerobic glycolysis was impaired, but that of the bat was unchanged. A decreased efficiency of phosphate esterification was found in mitochondria from brains of rats and bats irradiated at room temperature, but not of bats irradiated at 5° C.

The implications of these findings and their relationship to the existing literature are discussed.

Four tables.

Lethal Effect of ^{60}Co Gamma Radiation in Mice. F. Ellinger, with the assistance of B. F. Lindsley. Atompraxis **5**: 293–296, July–August 1959. (Naval Medical Research Institute, Bethesda, Md.)

It is shown that administration of Co gamma radiation under 4 π geometry requires for equal biological effect a considerable increase of the radiation dose measured in air as compared to that of 200 kvp given unilaterally (with a postero-anterior beam direction) and provision for saturation back-scatter.

The weight curves of mice irradiated with Co^{60} gamma radiation under the conditions of this experiment displayed no significant difference from pertinent observations made on animals exposed to 200 kvp.

The observation of this lesser effect of Co^{60} gamma radiation agrees in principle with the results of other investigators and previous studies by the author on guinea-pigs, but quantitatively the ratio of doses is not identical in these two animal species.

The species specific differences observed at 200 kvp exist, however, also in the case of the Co^{60} gamma radiation. The guinea-pig is in both instances the more radiosensitive animal species.

The present as well as previous investigations indicate the difficulties of extrapolation to man of animal studies concerned with the lethal effect of total-body irradiation. Further studies in other animal species are urgently needed in order to obtain appropriate base line data for the assessment of radiation hazards in man.

Co^{60} gamma radiation as employed in these experiments recommends itself for pharmacological studies in irradiated animals for the following reasons: (1) because of the possibility it affords of exposure of larger numbers of animals in one relatively short exposure, necessary for such studies; (2) because of the satisfactory reproducibility of lethal doses; (3) because of the absence of a notable influence of saline injections on these mortality rates.

Three figures; 2 tables.

The Mortality Response of the Burro (Equus asinus) to a Single Total-Body Exposure of Gamma Radiations from Zr^{95}/Nb^{95}. Bernard F. Trum, John J. Lane, U. S. G. Kuhn, and John H. Rust. Radiation Res. **11**: 314–325, September 1959. (B.F.T., Harvard Medical School, Boston, Mass.)

The LD 50/30 for burros irradiated at a rate of 15 r/hr. with gamma radiation from Zr^{95}/Nb^{95} sources was found to be 585 r with a 95 per cent confidence interval of 530 to 627 r. Lethally irradiated animals showed an absence of early deaths and an occasional prolonged survival time beyond thirty days. The greater number of deaths occurred between the twenty-second and twenty-fourth days, and no death occurred before the sixteenth day. The radiation syndrome was characterized by a latency of two weeks before prominent signs appeared. Subsequently, anorexia, loss of weight and deterioration in condition, ulceration of mucous membranes, prolonged bleeding from venipunctures, irregular gait, spasmodic head motion, and a few instances of irrational gnawing of skin on forearms or hocks were observed. There was no elevation of temperature, and the heart beat and respiration rate remained unchanged, except under conditions of exercise or agonal struggle.

The authors found variable I^{131} uptake by the thyroid, decreased iron uptake, increased blood pyruvic acid, and pancytopenia in the circulating blood of irradiated animals.

The lethality of gamma-irradiation from Zr^{95}/Nb^{95} was greater than that of gamma-radiations from Co^{60} or Ta^{182} if the free in-air doses were compared. The midline doses necessary to produce the same biological effects were about equal, however, for the various sources when all factors were considered.

Three figures; 6 tables.

Radiation Injury and Recovery in Swine. Bernard F. Trum, James N. Shively, U. S. G. Kuhn, and Walter T. Carll. Radiation Res. **11**: 326–342, September 1959. (B.F.T., Harvard Medical School, Boston, Mass.)

An experiment was planned to measure directly the injurious effect of sublethal doses of gamma-radiation in terms of life shortening. Sixty pigs were apportioned into six groups which were representative in sex, breed, and weight range (43 to 73 kg.). One group served as a control; the others were exposed to 360, 425, 484, 547, and 610 r, respectively. The exposures were made continuously from gamma-radiation of Zr^{95}/Nb^{95} sources in a large-animal exposure device at 1.4 r/hr. The animals were allowed ninety days of recuperation and then subjected to 50 r of gamma-radiation (Co^{60}) daily until death, at a rate of 33 r/hr.

There were no deaths in the ninety-day period after the initial irradiation. The first animal died on the eighty-third day of chronic irradiation and the last on the three hundred and eighty-fifth day. The mean survival times of the groups were related to the size of the initial irradiation. Residual or irreparable damage at ninety days post-irradiation measured in terms of survival to daily irradiation was not a constant percentage of initial dose. The dose at midcenter of the hog, calculated from measurements made within a hog carcass or a water-filled Lucite phantom, would have varied between 35 and 70 per cent of the measured air dose, depending on the size of the hog and its position in the radiation field.

One instance of lymphatic leukemia occurred in the experimental animals. Other clinical, hematologic, and pathologic changes were observed.

Five illustrations; 5 tables.

Effects of Gamma Radiation on Calves. M. O. Schultze, V. Perman, N. S. Mizuno, F. W. Bates, J. H. Sautter, H. S. Isbin, and M. K. Loken. Radiation Res. **11**: 399–408, September 1959. (M.K.L., Department of Radiology, University of Minnesota Medical School, Minneapolis 14, Minn.)

Twenty-seven calves were exposed to whole-body gamma-radiation from a Co^{60} source with a skin exposure dose rate of about 6.6 r per minute. The tissue exposure doses at the midline ranged from 150 to 360 r. None of the calves exhibited any immediate effect of radiation injury. About three days after irradiation a temporary diarrhea appeared, which usually subsided in about two days. The only exception to this was one calf which received 350 r; in this animal the diarrhea became progressively more severe, and on the fifth day the calf died—an "intestinal radiation death." In all the other animals receiving a tissue exposure dose at the midline of 250 r or more, an acute hypoplasia of the bone marrow and a hemorrhagic syndrome developed and death occurred after fourteen to twenty-four days.

Two calves exposed to 150 r suffered from a severe blood dyscrasia between the twentieth and thirtieth day, from which they recovered. The animals seemed to be normal by two hundred and seventy days.

The time sequence and extent of the changes in the circulating derivatives of the hematopoietic tissues were essentially the same as those described in other mammalian species.

Four photomicrographs; 3 graphs; 1 table.

Effects of Single Dose Proton Irradiation of Normal Skin and V×2 Carcinoma in Rabbit Ears. A Comparative Investigation with Protons and Roentgen Rays. Sture Falkmer, B. Larsson, and S. Sténson. Acta radiol. **52:** 217–234, September 1959. (University of Uppsala, Uppsala, Sweden)

For their experiments the authors employed a 185-Mev proton beam from a 230-cm. synchrocyclotron and a conventional 220-kv x-ray beam. Rabbit ears were irradiated with single doses, with observation of the effects at weekly intervals. The Bragg peak of the proton beam was used by employing Lucite absorbers.

The tumor effects of the two modalities were about the same, while the skin effect of the proton beam was somewhat less as judged on a semiquantitative basis.

These findings support the view that the proton beam, with its advantageous physical properties, may be used in the treatment of malignant tumors. Its disadvantage is the inability to get large field coverage without decreasing the depth-dose/surface-dose ratio.

Six photomicrographs; 3 diagrams; 2 tables.

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